QUINIDINE
in Disorders of the Heart

QUINIDINE in Disorders of the Heart

HARRY GOLD, M.D.

PROFESSOR OF CLINICAL PHARMACOLOGY AT CORNELL UNIVERSITY MEDICAL COLLEGE, ATTENDING-IN-CHARGE OF THE CARDIOVASCULAR RESEARCH UNIT AT THE BETH ISRAEL HOSPITAL, ATTENDING CARDIOLOGIST AT THE HOSPITAL FOR JOINT DISEASES, MANAGING EDITOR OF THE CORNELL CONFERENCES ON THERAPY.



PAUL B. HOEBER, INC
MEDICAL BOOK DEPARTMENT OF HARPER & BROTHERS

QUINIDINE IN DISORDERS OF THE HEART

A-Z

Printed in the United States of America

Preface

THIS monograph on the use of quinidine in the treatment of disorders of the heart is intended primarily as a guide for the general practitioner. Since emphasis is placed on a way of thinking about these problems and planning for them, it is my hope that both medical students and specialists in cardiology may find informative reading in it. Many of the observations and the methods advocated here are in complete agreement with those of others. Accordingly, the writings and views of others receive considerable attention. This is not, however, a review of the literature in the usual sense, but a personal account of knowledge based on experience with successes and failures, reading, and reflection in relation to this subject during a period of about twenty-five years; in the teaching of laboratory and clinical pharmacology to medical students; pharmacologic and clinical research; the care of several thousand cardiac patients in the hospital, clinic, and private practice; postgraduate medical courses; and lectures to groups and societies of medical practitioners of widely different interests, skills, and experience.

Observation has led me to the belief that only a small part of the potentialities of quinidine in disorders of cardiac rhythm is put to effective use, although these disorders are among the very common problems encountered in medical practice. The chief reason for this is the use of rigid stock methods rather than technics that are custom-built to suit the particular individual. What is often wanting is sufficient familiarity with the mechanism of the disordered rhythm and with the pharmacology of quinidine. These data, if properly integrated, lend flexibility to any method with

which treatment is started, and provide not only for rational beginnings, but also for rational changes in procedure indicated by the initial results.

In the presentation of the material, I have tried to pursue a fairly uniform plan: to define the particular physiologic mechanism to which quinidine is to be applied; to crystallize the precise therapeutic objective; to explain the particular action of quinidine on which dependence is being placed; to point out the sources of danger that may apply in special situations; to outline the doses with which treatment is begun with the intervals between doses, methods of adjustment and guides to adjustment in dosage; to discuss the complicating actions of the drug which may confuse the issue in a particular case; and to describe the toxic effects of quinidine and methods for their control. Particular emphasis is placed on the rationale of the practices that are advocated. An attempt has been made to clear certain matters by the account of case histories. Special sections have been included which deal with general principles applicable to the use of quinidine in all cases. Details of clinical diagnosis and prognosis have been kept at a minimum, and presented only where they seemed to be of some importance for a better insight into the problems of treatment.

In the account of the mechanisms of various disorders of rhythm and of the mode of action of quinidine, I have adopted formulations which are most commonly accepted. Many points on mechanisms are unsettled and involve controversial issues. I have utilized the concept of the circus movement in the explanation of some of the problems, although there is considerable evidence to the effect that the mechanism in a particular disorder may not be a circus movement, but multiple foci of excitation with asynchronism in the contraction of muscle blocks. I have

made use of the conventional concepts of the S-A node, A-V node, and conduction systems, although evidence has appeared which suggests that none of these applies to the human heart. As further knowledge is added and our understanding of mechanisms is better crystallized, some of the statements may need revision. The decision to do this was made in the interest of avoiding confusion and maintaining the length of the theoretical discussions within limits consistent with the text as a whole.

A selected bibliography, arranged chronologically, is appended. It is a limited one, and does not even include all of the best papers, but it should serve the purpose of directing the reader's attention to some of the more important literature bearing on special points mentioned in the text.

There is no doubt of the fact that there are particular patients in whom a disorder of rhythm cannot be controlled by quinidine. The considerations listed above help to discover who these are, and help to distinguish therapeutic failures due to the drug from those due to its improper application. The importance of judgment based on experience in the use of quinidine should not be underestimated, but in examining my own experiences in which a threatened defeat or disaster seemed to have been averted, I find that the responsibility for the result was usually to be ascribed to the application of one or another of the foregoing considerations. If I have described them sufficiently clearly, I shall have reason to hope that this monograph may succeed in enhancing the power of quinidine as an instrument of therapy in disorders of the heart.

To Professor McKeen Cattell I wish to express my appreciation of the generous number of hours he took from a crowded schedule to review the manuscript and especially to scrutinize the statements relating to basic

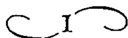
pharmacology and physiology. His comments have proved invaluable. It is a particular pleasure to express my gratitude to Dr. Theodore Greiner, one of our Research Assistants in Clinical Pharmacology during the tenure of a National Institute of Health Fellowship. He brought the fresh perspective of a recent medical graduate to bear on a critical examination of an early draft and rendered substantial aid in rephrasing sections to insure their intended meaning. To Dr. Leon J. Warsaw I am in debt for valuable help in the final revision of the manuscript, the reading of proof, and for the major work in the preparation of the index. I am also greatly obligated to Dr. Nathaniel T. Kwit and Dr. Walter Modell for their liberal assistance in the review of the more practical sections, the assembling and checking of bibliography, and the reading of proof. To my daughter Naomi I am deeply indebted for the arduous task of taking and typing dictation of the greater part of the preliminary draft of the text.

New York HARRY GOLD, M.D.

Contents

QUINIDINE

in Disorders of the Heart



Indications

WHILE the cinchona bark contains more than twenty alkaloids, the general discussions are based on quinidine alone. This is done so because quinidine is the most important member of the group in the treatment of disorders of the heart and the largest part of the clinical literature on the cardiac actions of this group of compounds relates to quinidine. All doses of quinidine, unless otherwise stated, will refer to quinidine sulfate, since this is the salt most commonly prescribed. It is well to bear in mind, however, that several of the cinchona alkaloids closely related to quinidine have received attention in regard to their actions on the heart and circulation, and are of importance in special cases in which quinidine itself cannot be used. These exert cardiac actions that are similar to quinidine, but there are significant quantitative differences, and there are some indications of qualitative differences. A more detailed discussion of the other compounds and the conditions under which they may be called upon is found in a later section.

Disorders of cardiac rhythm constitute the only indications for the use of quinidine in disturbances of the heart. It has no primary place in the treatment of cardiac pain or failure. There are some conditions in which quinidine prevents or abolishes cardiac pain or failure, but such results are due neither to direct dilatation of the coronary arteries nor direct action on the force of contraction of cardiac

muscle. When they occur, they are the indirect result of the prevention or abolition of one or another disorder of cardiac rhythm which in some individuals gives rise either to cardiac pain or failure.

The following is a list of the disorders of cardiac rhythm in which quinidine is effective:

1. Premature contractions or extrasystoles (auricular, nodal, ventricular)
2. Paroxysmal auricular tachycardia
3. Nodal tachycardia
4. Auricular flutter
5. Auricular fibrillation
6. Ventricular tachycardia
7. Ventricular fibrillation

It is perhaps well to call attention to the fact that not all of these disorders of rhythm always require treatment. For example, there are many patients in whom premature contractions are discovered in a routine examination, the patient being unaware of their presence. Many do just as well, and some better, when allowed to continue with these ectopic beats which are in themselves harmless. There is also the fact that some of these disorders of rhythm may be treated in other ways and by means of other drugs. The circumstances in the particular cases will determine the decision.

The disorders of cardiac rhythm present themselves in two general forms of therapeutic problems. The one concerns the patient in the midst of an ectopic rhythm which needs to be terminated and a normal rhythm restored. The other concerns the patient with a normal rhythm but with a history of repeated paroxysms of ectopic rhythm which need to be prevented. These two problems are often presented by the same patient.

Although a course of quinidine therapy to abolish premature contractions is usually carried out with the patient up and about, the restoration of a normal rhythm with quinidine in the case of the other disorders should rarely be attempted unless the patient is under close supervision and at rest. On the other hand, the prevention of attacks or recurrences is usually a problem of treatment in the ambulant patient.

I mentioned the fact that the indications for quinidine in cardiac disorders are the ectopic rhythms, and that these are among the very common problems encountered in medical practice. That about 25 per cent of an average cardiac population presents problems of disordered rhythm is probably a fair estimate. The number of these cases does not, however, satisfactorily reflect the importance of a drug which is effective in controlling them. A large proportion of patients with abnormal rhythm have a condition which is of no great consequence, affecting neither their ability to carry on nor their longevity. In many patients, the condition produces no symptoms and the disorder of rhythm may first be discovered during an examination for some other purpose. In fact, the onset of some patients' troubles often dates back to the time when the disorder of rhythm was called to their attention. There is, however, a sizable group in which the abnormal rhythm takes on the aspect of a serious disease. Among these, depending on the kind of disorder of rhythm, the type of patient, the condition of the heart, the following may result: cardiac neurosis, panic, palpitation, cough, attacks of syncope, cardiac pain, pulmonary edema, congestive failure, emboli, shock, and death.

2

Therapeutic Actions

IT IS probably only one basic action of quinidine *which accounts for the large number of therapeutic* applications of the drug in disorders of cardiac rhythm, namely, increase in refractoriness of the various cardiac structures. However, quinidine exerts many actions on the heart, the circulation, and extracardiac structures. It is necessary to bear this in mind in order to comprehend the wide variety of reactions which are observed in the numerous conditions in which it is used. The utility of the drug depends on the wide differential in doses necessary to affect different structures and to produce the various changes. It would hardly prove a useful drug in ventricular tachycardia, for example, if the same dose which suppresses the rapid ectopic pacemaker in the ventricle also suppressed the normal pacemaker of the sino-auricular node or stimulated the vomiting center. The fact that the rapid ectopic focus in the ventricle is relatively more sensitive to quinidine than the normal sinus node or the vomiting center accounts for the large number of cases in which ventricular tachycardia is uneventfully controlled. But patients differ, and there are some in which these differentials are either eliminated or reversed. Thus, undue sensitivity of the gastrointestinal tract is responsible for one of the limitations in the therapeutic usefulness of the drug, and undue sensitivity of the normal sinus pacemaker, approximating that of the ectopic ventricular pacemaker, accounts for one of

the serious hazards of the drug, namely, complete cardiac standstill with doses which are required to abolish the ventricular tachycardia. Many similar examples could be cited.

Familiarity with the basic actions of quinidine on the heart and other structures is very helpful in the therapeutic use of this drug for disorders of cardiac rhythm. While in the large proportion of cases the desired therapeutic action is dominant, and such simple dosage plans as will be described lead to the uneventful control of the cardiac disorder, there are many others in whom undesirable actions both on the heart and on extracardiac structures, so-called side-actions, intrude. An understanding of these is of material assistance in charting the course of therapy, especially in the case of the more difficult problems. Although there are many gaps in our knowledge of the basic actions of quinidine, enough information has been obtained from animal experiments and direct observations on man to afford a basis for understanding most of the common patterns of response during the therapeutic use of this drug. The more important effects and those most likely to be encountered in the routine use of quinidine are here listed.

1. Quinidine prolongs the refractory time of heart muscle. This has been determined in various ways. The essence of one experimental method consists of applying electrical stimuli at varying intervals of time to the rhythmically beating heart. When these stimuli fall far enough from the previous beat, they evoke a response; when they fall too near the previous beat, they fail to evoke a response. The longest time-interval between the normal beat and the extra stimulus which fails to call forth a response is one way of measuring the refractory time. The refractory time varies considerably from animal to animal, and with the rate of the beat. The refractory

period of the auricle has been found to vary under different conditions, from less than 0.1 to about 0.2 second. Quinidine may lengthen this interval between one beat of the heart and its readiness to respond to another stimulus by as much as 100 per cent. In another method similar information has been obtained by the effect of the drug on the peak rhythm of the isolated rabbit auricle. For example, without the drug the auricle might respond to rhythmic stimulation at rates up to 250 a minute, and at a rate of 260, there may be failures of response to some of the stimuli, quinidine might reduce the peak rate to 200 a minute with failures of response at rates above that. The extent of the lowering of the peak rate has been found to depend on the dose of the drug. This method has been utilized as a means of comparing the potency of various agents possessing a quinidine-like action.

2. Quinidine slows conduction in the heart muscle. The speed of conduction is determined experimentally in the intact heart by applying a stimulus to the heart, and recording the response simultaneously from two points on the heart. From the record of the difference in time between the responses at the two points and the distance between the two points, the speed of conduction is calculated. This also varies considerably with the rate and condition of the heart. The speed of conduction in the auricle has been found to vary from about 500 to 2000 mm. per second, under various conditions.

This action of quinidine is also observed directly in man by the use of the electrocardiogram: slowing of the circus movement in auricular fibrillation and flutter, prolongation of intraventricular conduction (prolonged QRS time), and prolongation of A-V conduction (prolonged P-R interval).

3. Quinidine exerts an antifibrillary action on the heart.

This has been observed in animals and directly in man. There is the observation that auricular fibrillation may be promptly terminated by a dose of quinidine, and ventricular fibrillation prevented. In animal experiments, a tetanizing current of sufficient intensity applied to the heart sends it into fibrillation. After quinidine, the heart is more resistant to the tetanizing current and now the intensity of the stimulus must be increased to send the heart into fibrillation. This effect is usually explained by the action of quinidine in prolonging refractory time, although some other type of action may be involved since there are substances which shorten refractory time and yet act to prevent fibrillation.

4. Quinidine depresses the excitability of heart muscle. In animal experiments, a threshold stimulus which evokes a response is no longer effective after the muscle has been exposed to quinidine.

5. Quinidine acts directly on the heart to depress rhythmic function. In animal experiments, it may slow the sinus rhythm after atropine, which indicates that it is a direct action and not one due to vagal stimulation. Also, high blood concentrations reached by very slow intravenous infusions, sufficient to block the vagus, may result in slowing of the heart. Sinus slowing is sometimes seen in humans. Quinidine also slows the rate of ectopic pacemakers, as in ventricular tachycardia in animals and man, and in larger doses may completely suppress the rhythmic activity of the entire heart.

6. Quinidine slows the electrical systole of the heart. This is detected by the prolongation of the Q-T interval of the electrocardiogram. The change may result from slowing of conduction or prolongation of the recovery phase. This effect may be observed in animals and man. What part it plays in the therapeutic or toxic actions of quinidine is not known.

period of the auricle has been found to vary under different conditions, from less than 0.1 to about 0.2 second. Quinidine may lengthen this interval between one beat of the heart and its readiness to respond to another stimulus by as much as 100 per cent. In another method similar information has been obtained by the effect of the drug on the peak rhythm of the isolated rabbit auricle. For example, without the drug the auricle might respond to rhythmic stimulation at rates up to 250 a minute, and at a rate of 260, there may be failures of response to some of the stimuli; quinidine might reduce the peak rate to 200 a minute with failures of response at rates above that. The extent of the lowering of the peak rate has been found to depend on the dose of the drug. This method has been utilized as a means of comparing the potency of various agents possessing a quinidine-like action.

2. Quinidine slows conduction in the heart muscle. The speed of conduction is determined experimentally in the intact heart by applying a stimulus to the heart, and recording the response simultaneously from two points on the heart. From the record of the difference in time between the responses at the two points and the distance between the two points, the speed of conduction is calculated. This also varies considerably with the rate and condition of the heart. The speed of conduction in the auricle has been found to vary from about 500 to 2000 mm. per second, under various conditions.

This action of quinidine is also observed directly in man by the use of the electrocardiogram: slowing of the circus movement in auricular fibrillation and flutter, prolongation of intraventricular conduction (prolonged QRS time), and prolongation of A-V conduction (prolonged P-R interval).

3. Quinidine exerts an antifibrillary action on the heart.

oral route, 0.8 Gm. or more. After intravenous doses, the cardiac acceleration may be partly nonspecific, resulting reflexly from the fall of the blood pressure. The partial vagal block in the A-V node is commonly seen in the form of acceleration of the ventricle during the use of quinidine to terminate an attack of auricular fibrillation.

Cardiac acceleration by quinidine appears to be possible as the result of still other mechanisms. It has been found that in the normal dog, an intravenous injection may produce extreme acceleration of the sinus rate when the vagi are intact, and *also after atropine or vagotomy. How the* latter comes about is unknown.

10. Quinidine causes a fall of systemic blood pressure. In those without hypertension, this rarely occurs to any significant degree after oral therapeutic doses. Intravenous doses, however, may cause a prompt and fleeting fall of blood pressure, which is sometimes quite marked and may be alarming. With a rapid intravenous injection of about 0.2 Gm. (3 gr.), the blood pressure may fall as much as 50 mm. Hg or more. This can be prevented by very slow injection. Direct action on the blood vessels to cause dilatation appears to account for the fall of blood pressure after moderate doses. Quinidine blocks epinephrine action on the blood vessels, and the vasodilator action of quinidine cannot be counteracted by epinephrine. After massive doses of quinidine, the fall of the blood pressure involves not only a peripheral dilator action, but also central vasomotor and cardiac depression.

There are several other actions of quinidine which are encountered in the therapeutic use of the drug, but since most of these are extracardiac, they are included in the next section which deals with side-actions and toxic actions.

7. Quinidine reduces the contractile force of the heart muscle. This may be demonstrated readily in isolated strips of heart muscle and in the intact heart in animal experiments. It is an action that is feared as a source of danger in the therapeutic use of the drug, but this action is rarely sufficiently developed in the range of doses in which quinidine is used for the control of disorders of cardiac rhythm to constitute a serious hazard. In the vast majority of cases other toxic effects lead to the discontinuance of the drug before any substantial interference with contractile force develops.

8. Quinidine produces ventricular tachycardia. This is seen in animals and occasionally in man. It usually occurs only after very large doses. The nature of the action involved here is unknown. As already stated, the usual action tends to depress rhythmicity and abolish ventricular tachycardia from other causes.

Very large doses of quinidine also cause ventricular fibrillation in animal experiments. The usual actions of quinidine give rise to a diametrically opposite result. The action of quinidine which brings about ventricular fibrillation is not understood; there is the possibility that extreme impairment of conduction or prolongation of refractory time may lead to functional fractionation of the muscle, which might give rise to fibrillation.

9. Quinidine blocks the vagus in the heart. When this action is unopposed by other actions of the drug, the heart rate (sinus rhythm) is accelerated. It appears to be an atropine-like action since, after sufficient doses, electrical stimulation of the vagus is no longer as effective in slowing the heart, and acetylcholine loses its effect. The cardiac acceleration occurs in man after both oral and intravenous doses, the effect being more pronounced after an intravenous injection and requiring fairly large doses by the

another; for example, if quinidine depresses rhythmicity and abolishes ventricular tachycardia, the action is therapeutic, but when the abolition of the ventricular tachycardia is attended by a long period of ventricular asystole causing syncope or a convulsion before the normal mechanism is restored, the action may be described as toxic.

Animal experiments show that the toxic effects of quinidine result not only from the total quantity of the drug but from a high concentration in the blood stream. After a rapid intravenous injection, as little as 25 mg. per Kg. may prove fatal, while after smaller doses given over a period of two hours, the fatal dose may increase to 100 mg. per Kg. This points to the danger of rapid intravenous injection.

The toxic effects of quinidine may be considered under two headings, those which may occur in persons who are not subject to disorders of rhythm, and those which are likely to occur only as the result of its use in an attempt to terminate an ectopic rhythm. A striking illustration of both types of toxicity in one person came to my attention a few years ago. It was the case of a young woman, 37 years old, who had rheumatic heart disease with mitral insufficiency, aortic stenosis and insufficiency, and marked enlargement of the heart. She had adequate functional capacity for strenuous activities when the rhythm was normal, but she was subject to paroxysms of auricular flutter with irregular rhythm due to varying A-V block and a heart rate of the order of 170 a minute. During some of these attacks, congestive failure developed. A daily oral dose of 1 Gm. (15 gr.) of quinidine sulfate seemed to provide protection against these seizures for a period of about 8 months, when, during the night following an evening of intemperance in food, drink, and dance, a paroxysm developed which was resistant to treatment. Her

3

Toxic Actions

THE terms toxic actions and side-actions are applied rather loosely in the case of quinidine, as in the case of most other drugs. The two terms are frequently used interchangeably, although it would be well to restrict the term toxic actions to those which are distinctly injurious. It is not possible to make a satisfactory classification of the actions of quinidine into therapeutic, toxic, and side-actions. There is no difficulty in labeling as a therapeutic action the prolongation of refractory time in auricular fibrillation, which results in the restoration of a normal rhythm. This is true for labeling as a toxic action an attack of ventricular fibrillation caused by quinidine. *There is also no difficulty in designating as a side-action the mild ringing in the ears since, while it may be annoying,* it is not particularly injurious. The proper classification of some actions presents more of a problem, as for example, the prolongation of the electrical systole. It is not known whether this is useful or harmful. In some cases, not its quality but its quantity determines whether an action is toxic or therapeutic; for example, depression of A-V conduction may be therapeutic when it serves to maintain a normal ventricular rate during the process of abolishing auricular fibrillation, but it is toxic when the degree of this action is sufficient to induce complete heart block. The circumstances in a particular case may also shift an action of quinidine from one class to

therefore, involved in attempting to reestablish the normal rhythm by additional doses, after a convulsion associated with the initial restoration by the smaller amount. The prolonged QRS time is indication of trouble ahead which can be prevented by discontinuing the drug as soon as this is discovered. Impaired hearing is indication for reducing the dose or discontinuing the drug, long before advanced deafness. When the rapid ectopic rhythm had been supplanted by a slow rhythm with coupling, the normal mechanism may have already been restored, and the slow irregular rhythm may now have been a toxic effect of the quinidine. This was intensified by additional doses to the point of the final disaster which may have been ventricular fibrillation.

Quinidine produces the well-known effects grouped under the term cinchonism, namely, impairment of hearing, ringing in the ears, blurred vision, lightheadedness, giddiness, and tremor. Quinidine acts on the central nervous system to produce convulsions; this is a frequent symptom in animals, but humans rarely receive large enough doses for this effect. The cases of convulsions after quinidine in humans are more apt to be due to cardiac asystole occurring in the course of the restoration of a normal rhythm.

Like other cinchona alkaloids, quinidine may cause gastric discomfort, nausea, vomiting, abdominal cramps, and diarrhea. The site of the emetic action may be local, due to irritation of the gastrointestinal tract occurring shortly after oral doses before appreciable absorption, or it may be central, occurring shortly after an intravenous injection. The doses employed are rarely sufficient to cause vomiting by the central action. Gastrointestinal symptoms which occur during the therapeutic use of quinidine are usually due to the local irritant action. There are wide individual differences

physician advised her, by telephone, to take 0.4 Gm. (6 gr.) of quinidine sulfate every hour until a normal rhythm was restored, and to judge the desired effect by a sensation with which she was familiar from her previous experiences. However, an unpredicted event took place, for, after a total of 42 gr., she suddenly developed a convulsion from which she promptly recovered. Shortly thereafter, she was found to have a normal rhythm of 90 a minute. During the day, the abnormal rhythm reappeared and quinidine was resumed in oral doses of 0.6 Gm. (10 gr.) every 2 hours. By the time a total of 92 gr. (including the original 42 gr.) had been taken, the patient was "stone-deaf." The heart rate had fallen from 170 to 84 a minute, but since the rhythm still appeared irregular due to coupling, an additional dose of 0.6 Gm. (10 gr.) was given. Three hours later, another convulsion developed, and this proved fatal.

Only one electrocardiogram was taken, and this after a total of 5 Gm. (60 gr.). It showed the auricular flutter with markedly prolonged QRS time (0.16 second). It may be noted at this point, that several of her electrocardiograms taken prior to the terminal episode, showed normal QRS time both during the attacks of flutter and during normal sinus rhythm.

It would be an error to regard this account as an indication of the danger of quinidine, for in the dosage employed in this case, all the common signs of minor toxic effects, which point to the need for discontinuing the drug, were passed by. The first convulsion was probably due to the fact that, when a rapid ectopic rhythm is suddenly brought to an end, a pause in the heart beat, sometimes of considerable duration, may take place before the normal rhythm is restored. The duration of the pause is apt to be increased by large doses of quinidine. An undue risk was,

ment of the contractile force of the heart with heart failure.

There are no specific antidotes to the toxic actions of quinidine. The fact that the major part of a large dose of quinidine is excreted within about twelve hours is a favorable factor in the event of serious poisoning.

There is no evidence of subtle chronic changes as the result of the prolonged use of even large doses of quinidine which produce no manifest acute toxic effects. Its actions are acute and reversible. They depend on the concentration of the drug in the blood stream and in the body.

The effects decline as the drug is eliminated. The effects disappear within about twenty-four hours or less, whether a particular dose, large or small, is taken for days or years. We now have several patients who have used quinidine regularly in daily doses of 2 to 4 Gm. (30 to 60 gr.) for periods of years for the control of troublesome disorders of rhythm. One of these with hypertensive and arteriosclerotic heart disease took a daily dose of 4 Gm. of quinidine for the control of a paroxysmal disorder of rhythm during a period of fourteen years, and in this period he consumed about 20 Kg. of quinidine. None of these presented changes which might implicate the chronic action of a drug.

The untoward effects of quinidine occurring only in patients with disorders of cardiac rhythm are discussed in the special sections.

in susceptibility to these actions. They are infrequent with single doses of less than 0.8 Gm. (12 gr.). Patients are occasionally encountered in whom a few doses of 0.2 Gm. (3 gr.) cause cramps and diarrhea. The majority of individuals, however, tolerate such doses as 2 to 3 Gm. daily, and many even larger amounts, without gastrointestinal discomforts. The gastrointestinal symptoms are sometimes overcome by giving the dose together with meals, or by suspending the drug in compound chalk mixture to diminish its local irritant action. In cases in which gastrointestinal discomforts preclude effective oral therapy, quinidine in propylene glycol by the intramuscular route may be substituted (see section on Preparations).

A rare toxic state is seen in humans with the appearance of shock and respiratory distress for hours before the fatal termination. The site of this action is not established. It may be a manifestation of the central action seen in animals after large intravenous doses, which cause primary stimulation of the central nervous system with convulsions followed by secondary depression of the respiratory and vasomotor centers. It has been suggested that caffeine may be effective in overcoming the respiratory depression.

Idiosyncrasies to quinidine exist in the form of urticaria, purpura, asthma, and changes in the cellular elements of the blood. These are very rare, and in some instances may be avoided by the use of other members of the cinchona group. A rare case of thrombopenic purpura, giving rise to bleeding, has been described occurring within an hour after 0.1 Gm. of quinidine. It was rapidly counteracted by a transfusion of citrated blood.

Side-actions or toxic actions on the heart include prolongation of A-V conduction, with varying grades of heart block, intraventricular block, premature contractions, ventricular tachycardia, ventricular fibrillation, and impair-

may be prolonged to about 0.12 second, and a bundle branch block with a QRS time of 0.12 second may show prolongation to 0.16 or 0.18 second. It is not wise to increase the dose beyond such points. The electrocardiogram with bundle branch block does not appear to be more sensitive than the normal to prolongation of the QRS time. Massive doses may spread the QRS time, as indication of impairment of intraventricular conduction, until the QRS loses the contour of a normal ventricular group. This is a precursor of ventricular fibrillation and represents severe poisoning of the myocardium. Such tracings may show no P-waves due to auricular arrest.

In addition to the foregoing, there are on occasion the few toxic rhythms caused by quinidine, which have already been mentioned: ventricular premature contractions, ventricular tachycardia, and ventricular fibrillation.



Absorption, Blood Levels, and Elimination

THE absorption of quinidine after oral administration on an empty stomach is fairly rapid, and the elimination is also rapid. This has been shown by study of the curve of blood concentration of the drug. After a dose of 10 mg. of quinidine alkaloid per Kg. in

4

Effect on the Electrocardiogram

QUINIDINE can produce changes in all the components of the electrocardiogram, but the electrocardiogram is not a very sensitive indicator of the actions of this drug, and in the vast majority of cases in which the drug is used effectively for the control of disorders of rhythm there are no conspicuous changes in the electrocardiogram. This, of course, leaves out of consideration the therapeutic change which occurs with the abolition of an abnormal and the restoration of the normal rhythm. Other than these, changes usually take place only after very large doses. There is no electrocardiographic pattern peculiar to quinidine action.

The P-waves are sometimes widened. The P-R intervals may be prolonged. The T-waves sometimes become lower, broadened, or umbilicated, occasionally inverted, and sometimes a positive T-wave becomes higher. A peculiar effect on the T-wave which we observed in animals was the tendency for a negative T-wave to become less negative, and as the dose was increased, to become a high positive T-wave. The Q-T interval may be prolonged.

One effect on the electrocardiogram which is of practical importance is the prolongation of the QRS time When it occurs, it usually begins after a daily dose of about 2 to 3 Gm. A normal QRS time of about 0.08 second

drug reached 1 mg. per liter of plasma or more the ectopic rhythm was brought under control.

Attempts to correlate the actions of quinidine with the concentrations of the drug in the blood are in the preliminary stage at the present time. They offer promise of yielding important information relating to the therapeutic use of quinidine and its allied compounds in disorders of cardiac rhythm.



Tolerance

THE natural susceptibility to quinidine on the part of the majority of individuals falls within a sufficiently narrow range to make it fairly simple to establish satisfactory routine dosage plans. However, the extremes are fairly wide apart. How this matter stands with respect to the fatal action in man is unknown, but in regard to lesser effects on the heart, brain, and gastrointestinal tract, there is a great deal of experience. At one extreme, there is the patient in whom a single dose of 0.3 Gm. (5 gr.) of quinidine produces diarrhea or ringing in the ears. At the other, there is the patient in whom these effects appear only after a daily dose of 5 Gm. (75 gr.). There is at one end of the scale the patient who remains free of paroxysms of auricular fibrillation with a dose of 1.0 Gm. (15 gr.) daily, and at the other end, the patient

normal adults, the drug is detected in the blood stream in the first hour, its concentration rises to a maximum of about 2 to 3 mg. per liter of plasma in two to three hours, and then declines in the ensuing hours to a level of the order of 10 per cent of the peak concentration at the end of twenty-four hours. There is indication that the curves are essentially similar for cinchonidine, somewhat higher for quinine, and about one-half as high for cinchonine. Food in the stomach interferes with absorption, so that the concentration in the blood is lower when the drug is taken after meals. Traces appear in the urine within about thirty minutes after the dose, and the drug usually disappears from the urine in about twenty-four hours. About three-fourths of the dose is destroyed in the body, and the larger part of the remainder is excreted in the urine.

The curve of quinidine action after an oral dose, as measured by the slowing of the circus movement in patients with auricular fibrillation, parallels the major part of the curve of the concentration of the drug in the blood, except in the areas of subthreshold levels. A distinct effect is present within about one hour, the maximum effect develops in about two to four hours, a plateau persists for about two more hours, then the effect begins to decline, and usually disappears in about twelve to eighteen hours.

There are some observations indicating a correlation of the concentration of the drug with certain effects. It has been observed in dogs, following the slow intravenous injection of quinidine, that the cardiac vagus is completely blocked when the concentration of the drug reaches 7.4 mg. per liter of plasma. The corresponding level in the case of cinchonine is 13 mg.; with cinchonidine, 13.3 mg.; and with quinine, 19.8 mg. Similar observations made in patients with paroxysmal nodal tachycardia after oral doses of quinidine showed that when the concentration of the

clined to believe that these represent physiologic adjustments rather than true acquired tissue tolerance, since the symptoms reappear when the same dose is given following an interruption of treatment for a day or two. Among our patients who have used quinidine for long periods of time, we had one who took a dose of 4 Gm. (60 gr.) daily for fourteen years. This regimen kept his attacks of auricular flutter and fibrillation in abeyance except for brief test periods when the drug was withheld. In the fourteenth year with this dosage, there were periods of escape. An attempt to control these by increasing the dose to 5 Gm. (75 gr.) daily proved ineffectual and resulted in impairment of hearing and blurring of vision. These symptoms had been produced by test doses of this size in the early period of treatment, so that no tolerance had developed in that area of the drug action. However, the escape of paroxysms of auricular flutter and fibrillation became increasingly more frequent, which might suggest increased tolerance of the heart to quinidine. Again, I do not believe this to be a tissue tolerance acquired as the result of the prolonged use of the drug but as the result of progression of his hypertensive and arteriosclerotic disease. The fourteenth year of treatment was his last. He developed a cerebral hemorrhage and congestive failure, and the auricular fibrillation which had been paroxysmal became fixed. This change in the behavior of auricular fibrillation occurs in patients who have not had quinidine. Under these conditions, it is also well known that quinidine is often ineffectual in restoring a normal rhythm even if the drug had not been used before.

in whom a dose of 4 Gm. (60 gr.) daily is essential to achieve a similar result. Special tolerance may be similar in different organs. We had under treatment a patient with paroxysmal auricular fibrillation whose heart showed inordinate tolerance to quinidine so that a daily dose of 4 Gm. (60 gr.) was necessary to eliminate the paroxysms. His central nervous system also showed great tolerance, only when the dose was increased to 5 Gm. (75 gr.) daily did he develop a sense of lightheadedness, impairment of hearing, and clouded vision. This, however, is not always the case. An unusual degree of susceptibility may apply to only one organ while others remain very tolerant. This sometimes presents a serious obstacle to the therapeutic use of quinidine. An example is the patient in whom a single dose of 0.6 Gm. (10 gr.) produced buzzing in the ears but 4 such doses at three-hour intervals were necessary to terminate an attack of auricular fibrillation.

There are patients with natural allergy to quinidine. In these, small doses give rise to skin eruptions, purpura, asthma, changes in the cellular elements of the blood, and other reactions. These must be very rare, and although mentioned in the literature, I have never encountered them.

The question of acquired susceptibility or tolerance to quinidine as the result of prolonged use of the drug is sometimes raised. As far as I am aware, proof of this phenomenon does not exist. I have patients who have taken 2 to 4 Gm. (30 to 60 gr.) of quinidine daily for years for the control of troublesome disorders of rhythm without indication that the prolonged use had created a state calling for smaller or larger doses. There are occasional cases in which the necessary therapeutic doses give rise to mild visual or auditory disturbances in the early period of treatment, which subside as the therapy is continued. I am in-

dition as to hazard poisoning with quinidine. I shall not consider here the fear of danger from larger doses, but attention may be focused at this point on the use of an ineffectual daily dose of quinidine for a period of four months. Does such a practice bear any relation to the nature of the action of quinidine, its speed of elimination, and the curve of cumulation? How long does it take to discover that a particular dosage plan is inadequate, and that the drug should either be abandoned or something else be done about it? This illustration refers to the use of the so-called "average dose." I have encountered instances of a similar nature in which the physician broke with the tradition of the "average dose," and used as much as 2 Gm. (30 gr.) daily for several weeks without avail and then sought advice. The new point here is the large dose: Does this patient show any signs of toxicity, gastrointestinal discomforts, impairment of hearing, tinnitus, or clouding of vision? Does the electrocardiogram show any significant prolongation of the QRS time? Does quinidine produce any subtle damage in the body, which may suddenly appear without warning after the drug has been used in large amounts over a long period of time?

The use of inflexible systems of dosage is responsible for a large share of the defeats in quinidine therapy, and some of the disasters. A dose of a few grams of quinidine in the more tolerant individual involves no greater risk than a few grains in the more susceptible one. How much the patient is taking is not the decisive question, but what that amount is doing. If it fails to produce therapeutic effects, there is need for more; if toxic effects have resulted, there is indication for less. The dose of quinidine cannot be defined in terms of an amount of drug, but in terms of an objective and a plan for achieving it, the objective being to bring the abnormal rhythm under control without toxic

7

Dosage*

DOSAGE is the most important link in the chain of problems comprising the successful use of a drug. This applies to all drugs, and in the case of quinidine, it appears to be the weakest link. It is infrequent that I find quinidine applied to the wrong conditions, but this is not the case with respect to dosage. What is the nature of the difficulties? The point which is at once apparent is an unwarranted concern with the number of grains or grams the patient is receiving. Numerous illustrations can be cited. A patient consulted me about some strange sensations in the chest in which she felt the heart suddenly "flop over," land in her throat, and produce a cough. It turned out to be a case of rheumatic heart disease in which the presenting symptoms were due to premature contractions. I wrote her family physician recommending the use of quinidine for their control. He telephoned me to say that we should have to devise some other treatment, since quinidine was what she had been receiving, 0.2 Gm. (3 gr.) three times a day for the past four months, and the symptoms had continued. The advice to increase the dose was accepted with reluctance, because 3 gr. was the "average dose" of the Pharmacopoeia, three times daily was a commonly recommended plan of administration, and premature beats are not so serious a con-

* The system of metric doses and approximate apothecary equivalents adopted by the U. S. Pharmacopoeia is used in this text.

individual. It is not wise to attempt to abolish a disorder of cardiac rhythm with a single dose of quinidine, although the first small dose may have this effect in a very sensitive individual. Patients differ too widely in their susceptibility to this drug and a single dose which will prove effective in any considerable proportion of patients, is likely to entail unwarranted risks in others. The highest incidence of therapeutic results with the lowest incidence of serious toxicity in the case of quinidine is assured by an appropriate cumulative system of dosage. The treatment is started with a dose that is known to be safe, and one that, by itself, is likely to prove ineffectual. The peak effect of the oral dose develops in a period of about two to three hours. The dose is, therefore, repeated every two to three hours in order to pyramid the effect of one dose on that of the previous dose. During the course, the patient is observed before each dose in order to determine whether the objective has been attained. In this way, the intensity of quinidine action on the heart increases gradually and by safe steps until the action is sufficient to produce the therapeutic result, or minor toxic effects occur which preclude the further use of the drug.

The minor toxic effects have already been described. Intervals between doses shorter than two hours are unwise because if the next dose is given before the full effect of the previous one has developed the patient may receive more doses than are necessary. Intervals significantly longer than three or four hours delay the development of the required intensity of quinidine action on the heart, since the next dose is being added after partial recovery from the previous one due to the rapid elimination of the drug. If the problem is less urgent and the patient cannot be so closely observed, intervals between doses as long as six hours may be used. A dose given three times daily with

effects. Each patient presents a special problem. For example, the case of the patient who, while lying in the hospital with a coronary thrombosis, suddenly goes into shock with an attack of ventricular tachycardia, is clearly different from that of the patient who is up and about and working, but who once or twice a week develops an attack of auricular fibrillation usually lasting only an hour or two, which sometimes causes him to faint. Each case calls for a special strategy which can easily be worked out if due consideration is given to the peculiar clinical features of the particular case and a few basic facts concerning the action and behavior of quinidine.

At this point, it may be well to note how the use of quinidine in disorders of cardiac rhythm differs from most other forms of therapy. It involves a kind of all-or-none result. Consider for comparison some of the common therapeutic agents. When digitalis is used for the relief of heart failure, a moderate dose will produce some therapeutic effects, a larger dose greater therapeutic effects; so also in the case of diuretics for the control of edema, or morphine in the treatment of pain. The matter is essentially similar when quinidine is used to prevent recurrences of some disorder of rhythm; a particular dosage may be inadequate to abolish all attacks, but may suffice to reduce their number or frequency, and this is a partial therapeutic result. It is otherwise, however, when quinidine is used to terminate an attack of a particular disorder of rhythm. Here there are no graded results; the therapy is either a complete success or a complete failure.

The dosage plan which makes it possible for the heart to receive the precise concentration of the drug necessary in the particular case, is the deciding factor.

Enough has been said to indicate that the effective dose of quinidine is unknown. It has to be determined for every

daily dose is a self-limiting process. In the case of digitalis, the use of a daily dose of 0.2 Gm., for example, shows increasing intensity of action over a period of about three weeks, when a level is reached beyond which the effect will not increase regardless of the length of time the same daily dose is continued. The same principle applies to quinidine, but in the case of this drug, cumulation comes to an end in a period of four or five days. If treatment is begun, therefore, with a daily dose of 1 Gm. (15 gr.), taken as 0.3 Gm. (5 gr.) at intervals of six hours, and the abnormal rhythm is still present after the first day, the same dose should be continued for four or five days, for during that period the intensity of action will increase. In the event the therapeutic effect does not appear at the end of five days, it will serve no purpose to use that dose any longer for, from that point on, the intensity of quinidine action will remain unchanged. The daily dose is then increased and the new dosage is tested in a similar manner. This system of increasing the daily dosage every five days is continued until a level of dosage is reached which is effective in bringing the abnormal rhythm under control. By the same token, if the effective daily dosage fails to produce toxic effects after five days, it may be continued indefinitely with little risk of toxicity.

Thus far problems of dosage have been considered only in relation to one part of the task, namely, that of terminating an ectopic rhythm and restoring a normal one. The other part is that of maintaining the result, preventing a recurrence, or preventing attacks in the paroxysmal types of ectopic rhythm. The special features of dosage applicable to these will be discussed in the next section.

none during sleep is a convenient and often effective method of treatment in ambulant cases.

The size of the individual doses usually ranges from 0.2 to 0.6 Gm. (3 to 10 gr.), depending on the urgency of the condition, the kind of supervision that is feasible, and the result of initial experiences with the patient. Special regimens will be discussed in the sections dealing with the particular disorders of rhythm. A dose of 0.4 Gm. (6 gr.) every two to three hours is a satisfactory routine with which to begin treatment for terminating a disorder of rhythm in a patient under close supervision. Smaller "test" doses have been advocated but I have never encountered any need for them. The dose may be increased to 0.6 Gm. (10 gr.) after several doses of the smaller size have failed to reveal any undue sensitivity to the drug, and in more urgent cases, the treatment may be carried out from the start with 0.6 Gm. (10 gr.) every two to three hours. These doses are safe enough as the initial ones, and as increments to nontoxic levels of quinidine action from previous doses, they are not likely to produce serious toxicity. The total amount of the drug required to terminate a disorder of rhythm may be large or small, but even if large it is without danger, for protection against overdosage is inherent in the technic, calling as it does for the discontinuance of the drug at the first signs of undesirable effects.

I have made mention of the fact that a dose of quinidine three times daily (intervals of about six hours) is often expedient in ambulant patients. It is particularly applicable to patients with premature contractions. This treatment is usually begun with 0.3 Gm. (5 gr.) three times daily. How long is this dosage continued if it is ineffective? In this connection, a special feature of quinidine cumulation needs to be considered. As in the case of many other drugs, such as bromides or digitalis, quinidine cumulation with a fixed

it subsides promptly when she lies down with the head lower than the legs. Her only problem is to prevent the attacks. A man 44 years old with hypertensive and arteriosclerotic heart disease has for several years been subject to seizures which are sometimes auricular flutter and at other times auricular fibrillation. They last only a few hours and give him no concern except for the fact that they recur almost daily and some of the seizures cause him to faint. On several occasions he fell and sustained bodily injuries while at work. These experiences have been so unpredictable that he has had to discontinue his occupation for fear of falling and sustaining a serious injury. Again, the presenting problem is not that of terminating an attack, but preventing recurrences.

The details of the management of these problems are discussed in the sections dealing with the specific disorders of rhythm. Only the more general aspects of maintenance or prevention will be considered here.

The two case histories related above clearly represent patients with paroxysms of ectopic rhythm in which there is no doubt of the need for the prevention of attacks. This is not, however, always the case. In many instances there is, indeed, the question whether an attempt should be made to prevent recurrences with quinidine, whether it is not more practical to allow the patient to develop attacks and treat each as it occurs, because they occur so infrequently or produce relatively inconsequential disturbances. There are obstacles in the way of systematic prophylaxis in these cases. It is a matter of no difficulty to excite a patient's enthusiasm for a course of quinidine therapy just after a few severe paroxysms that have occurred in a period of a week or two, but it is difficult to sustain this cooperation in the continued daily use of large doses of quinidine for periods of many months in which there is freedom from

8

Maintenance and Prophylaxis

DISORDERS of cardiac rhythm are either continuous or paroxysmal. In some patients, an ectopic rhythm may come and go spontaneously over periods of years. In others, a particular disorder of rhythm once established, continues indefinitely unless special measures are taken to interrupt it. In some of these, the restored normal rhythm persists without further treatment, but in the majority there is a tendency to recurrence after shorter or longer intervals, from hours to years. Some patients present the physician with two problems: to terminate an attack of ectopic rhythm and then to prevent a recurrence. Others present only one problem, that of prophylaxis, the prevention of paroxysms of ectopic rhythm. In the latter group, the abnormal rhythm itself may be of little consequence. It may be very fleeting or may be easily terminated by the patient. The disability arises from the fact that it keeps recurring. A few examples of the latter might be cited. A woman 46 years old with rheumatic heart disease and mitral stenosis has for several years been subject to paroxysms of auricular tachycardia. They come and go as often as several times a day. Each attack causes a sense of giddiness and fear of fainting, which leads to panic when she happens to be where she cannot lie down. She requires no help in terminating the seizure, for she discovered that

restore the normal rhythm. Some observers have questioned the utility of these smaller maintenance doses. They are undoubtedly sometimes successful, but often they fail. It is my observation that the doses of quinidine necessary for maintenance or prevention are often as large as, or larger than, those required to terminate an attack. This is not at all remarkable when one considers the fact that during the course of treatment to abolish an attack the patient is apt to be at rest or in bed, while maintenance or prevention is usually carried out in the ambulant stage. It is probable that the wider range of experiences, emotional and physical, to which the patient is exposed when he is up and about and working, gives rise to factors which break through the milder grades of quinidine action on the heart. On the face of it, the need of larger doses of quinidine for maintenance than for abolishing an abnormal rhythm seems to differ from the principle of therapy in the case of digitalis where one almost invariably uses larger doses to abolish the failure and smaller doses to maintain the gains.

When the matter is considered in terms of the speed of elimination of the drugs, however, the difference is only apparent. In the case of digitalis, the object is to establish a high degree of action by large doses, and small doses suffice to maintain the level because the drug is slowly eliminated. In the case of the rapidly eliminated digitalis glycosides, the daily maintenance dose approaches the full digitalizing dose. Such is often the case in the use of quinidine which is rapidly eliminated; the maintenance dosage to prevent the recurrence of an ectopic rhythm is often the same as that necessary to abolish the attack. The analogy with digitalis extends further. It is not uncommon to find that a daily dose of digitalis which suffices to maintain the failure under control and the apex rate in auricular fibrillation at about 70 a minute, when the patient is at

attacks. The fact remains that in the attempt to give quinidine for prevention in cases with infrequent paroxysms, the use of the drug is often interrupted and the attacks recur.

In some respects, the prophylactic use of quinidine presents greater difficulties than its use in abolishing an attack. I have already stated that the use of quinidine to terminate a seizure of ectopic rhythm is usually a procedure to be carried out with the patient at rest and under close supervision, while its use for prevention is an ambulant form of therapy. The prophylactic use of the drug has the advantage of greater safety, even though in this case the patients cannot be subjected to the same degree of supervision as those confined to bed. The reason is that in preventive therapy, quinidine is usually given in the presence of a normal rhythm, the only danger being the direct toxic effects of the drug. These are well known and easily controlled by reduction of dose. On the other hand, in the use of quinidine to terminate an attack, there are additional sources of danger, such as the very rapid tachycardias which sometimes occur in the intermediary stages between the abnormal and the normal rhythm, the long pause in the activity of the heart after the abnormal rhythm is interrupted and before the normal rhythm is resumed, other types of unfavorable action on rhythm which are discussed in another section, and the possibility of the discharge of emboli when the auricles begin to contract after fibrillation has persisted for some time.

The matter of dosage in prevention presents a special problem. After quinidine has satisfactorily terminated an attack of ectopic rhythm, it is customary to prescribe a maintenance regimen to prevent recurrences. The doses that are given are usually smaller than those used to

with the patient at rest, was responsible for the restoration of the normal rhythm was confirmed by the fact that a similar rest period during 5 clinic visits without the drug had no influence on the abnormal rhythm.

The foregoing is clearly a case in which a paroxysm of auricular fibrillation or flutter is very sensitive to quinidine when the patient is at rest, but in which the factors prevailing during activity are highly antagonistic to the cardiac action of the drug; a single dose of 0.6 Gm. (10 gr.) sufficed to terminate an attack during rest, but as much as 3.3 Gm. (50 gr.) daily was not sufficient to prevent recurrences during activity. Since larger daily doses produced symptoms of cinchonism, the drug proved to be impractical as a prophylactic measure in this patient.

In patients with a paroxysmal disorder of rhythm in whom the presenting problem is to prevent attacks, it is my usual practice to begin with a daily dose of 1 Gm. (15 gr.) in the form of 0.3 Gm. (5 gr.) three times daily. If and when an attack occurs, the daily dose is increased by 0.3 Gm. (5 gr.). This is usually accomplished by first shortening the interval between doses, and then increasing the size of the individual doses. This system of increasing the size of the daily dosage after each attack is continued until a level is reached at which paroxysms no longer occur. The required daily dosage varies greatly. In some the initial dosage of 0.3 Gm. (5 gr.) three times daily is sufficient. In more stubborn cases, as much as 0.6 Gm. (10 gr.) every three hours, or about 4 Gm. (60 gr.) daily, proves to be necessary.

Any number of variations of this general plan may be employed with advantage. Previous experience with quinidine in the particular patient, or urgency of the condition, may indicate a more intensive system at the start, larger doses and shorter intervals. If, for example, the attacks tend to come in the late afternoon during the period of

rest, is insufficient for either when the patient is up and about and working. Under these conditions larger doses of digitalis are necessary. This corresponds to the experience with quinidine in which larger doses are necessary for prophylaxis in the ambulant patient than to abolish an attack in the patient at rest.

An interesting case may be cited in this connection, in which an experiment was performed to demonstrate this observation. A male patient, age 26, with rheumatic heart disease, mitral insufficiency, enlarged heart, and fairly normal functional capacity, was subject to paroxysms of auricular fibrillation and flutter for two years. In the endeavor to control these, quinidine was given and the dosage was gradually increased until he received 3.3 Gm. (50 gr.) daily, or 0.6 Gm. (10 gr.) at approximately three-hour intervals. The attacks continued to recur, and larger doses exceeded his tolerance, producing dizziness, mild deafness, and ringing in the ears. An experiment was carried out to determine the single dose of quinidine which, during a paroxysm of auricular flutter or fibrillation, would establish a sinus rhythm. Accordingly, quinidine was discontinued. When the patient returned to the clinic during one of the attacks, an electrocardiogram was taken, a dose of 0.6 Gm. (10 gr.) of quinidine was given by mouth, the patient rested quietly, and additional electrocardiograms were taken at intervals of an hour. This dose sufficed to establish a normal rhythm within one to two hours in 4 of 5 such tests carried out during a period of six weeks. Yet in a period of sixteen months the ectopic rhythm was present during 14 of the 17 visits, although throughout this period he took from 2 to 3.3 Gm. (30 to 50 gr.) quinidine daily in capsules of 0.6 Gm. (10 gr.) each, at approximately four-hour intervals, the last dose being taken about two hours before the examination. That the single dose of 0.6 Gm. (10 gr.) taken during the previous tests

already suffered so much in the previous three years, and if he had not been informed of the rationale of the procedure and forewarned of a possible long period before the desired results could be achieved. The desirability of informing the patient in advance of the nature of the plan and of the possibility of a protracted course before the proper dose is established cannot be overemphasized.

Whatever the necessary dosage turns out to be, if it produces no toxic effects when given for four or five days, there is little risk of further cumulation or toxicity if it is continued indefinitely. There is no way of knowing in advance how long the treatment will be necessary in any particular patient. In some, the need disappears in a short time as in patients with active rheumatic carditis in whom the activity subsides, or in patients with acute coronary thrombosis after adequate restoration takes place. In others, the need for the drug remains indefinitely. The answer is supplied by test periods in which the drug is withheld.



Premature Contractions

PREMATURE contractions or extrasystoles represent the most prevalent type of ectopic rhythm. They occur very commonly in persons with an otherwise normal heart. In these, they are frequently related to storms of emotion or protracted periods of

greatest stress, protection is concentrated by larger doses preceding and during those periods. The pattern of the attacks in the particular individual will often point the way to significant modifications of the general plan.

The length of time it takes to establish the required dosage to prevent recurrent paroxysms of ectopic rhythm is extremely variable. Since every step in the procedure depends on the occurrence of an attack, the frequency of attacks in the particular case is a decisive factor. If attacks occur two or three times a day, it may be only a matter of a few days before the effective daily level is reached. On the other hand, if attacks occur at an average interval of about a month, several months may elapse before the necessary dosage level is discovered. For example, in one patient, 39 years of age, with paroxysmal auricular fibrillation, the attacks occurred at an average interval of approximately thirty-five days. They were very disturbing. They produced a sense of severe palpitation and sufficient faintness to make it necessary for him to interrupt his work for a day or two. For a period of three years he had visited many clinics and private physicians, and had become quite convinced of the uselessness of digitalis and quinidine. Nevertheless, quinidine was started with 0.3 Gm. (5 gr.) three times daily. When the first attack occurred which was in twenty-three days, the dose was increased until the next attack, which occurred in eighteen days. In this manner, the daily dosage was increased after each attack until he received 3 Gm. (45 gr.) daily, when all attacks ceased. Nearly six months elapsed before the necessary daily dosage was established. In the light of greater experience, it would have been possible to achieve this result in about one-half the time by larger steps, but even then, it is doubtful that the patient would have cooperated in a course of therapy with such suggestion of futility, if he had not

more serious disorder of rhythm, ventricular tachycardia. It is well to treat them even though the patient is not aware of their presence.

There are several measures employed in the control of premature contractions. Quinidine is by far the most useful, and is effective against all forms, those of auricular, nodal, and ventricular origin. A satisfactory routine dosage for adults is 0.3 Gm. (5 gr.) of quinidine sulfate in the form of a capsule or tablet three times daily. It is an ambulant form of therapy. An intensive cumulative system of dosage is rarely necessary against premature beats because this disorder of rhythm rarely presents an urgent problem. As in all cases, there are marked individual differences in susceptibility to the drug. In some, the abnormal beats may be brought under control by smaller daily doses, while in many, much larger daily doses are necessary. In the typical case in which the daily dose of 1 Gm. (15 gr.) is adequate, the premature beats will disappear after the first day, or after treatment for a period up to four or five days. During this period, a moderate degree of cumulation takes place resulting in a progressively increasing concentration of the drug to which the heart is exposed. As has been stated in the section on Dosage, the curve of cumulation with a fixed daily dose of quinidine flattens out by the fourth or fifth day, and if by that time the premature beats persist, it is evidence that the daily dosage is too small, and that the abnormal rhythm is likely to persist, no matter how long beyond that point the same daily dose is continued. The dose is then increased to 1.3 Gm. (20 gr.) daily (5 gr. every four hours) for four or five days, and in this manner, the increase in daily dose is continued to 25 or 30 gr. or more, until a dosage level is reached which is effective in controlling the premature contractions. That dosage is continued indefinitely for purposes of maintenance. It may

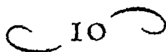
nervous tension. Reflexes from the biliary or gastrointestinal tract may give rise to them. They are also brought on by factors operating in organic heart disease, such as the toxic or cellular changes of active rheumatic carditis, or the anoxia of coronary insufficiency, or the distension of the auricle or ventricle in hypertensive disease. The premature beat may arise from any portion of the heart, the S-A node, the A-V node, the auricles, and ventricles. Detection of the site of origin is of some practical significance. For example, when, during the use of digitalis, a patient develops premature beats, it becomes a matter of importance to decide whether they are due to the heart failure and possibly insufficient digitalis, or to excessive digitalization. The discovery in the electrocardiogram that the premature beats are of auricular origin rules out digitalis poisoning as the cause, since the beats produced by digitalis are almost invariably of ventricular origin.

Not all cases of premature contractions require treatment. There are those in whom the premature beats cause symptoms, such as a sense of palpitation, hacking cough, strange sensations in the chest, throat, or head. They may give rise to undue cardiac awareness and apprehension. Such patients are treated. Many of these, however, prefer to carry on without treatment, once they are assured that the ectopic beats are without danger and do not represent or cause serious cardiac disease. In a large proportion of the cases, the premature contractions cause no symptoms, the patient being unaware of them and their presence being discovered in the course of an examination for other purposes. Since premature beats are without harm to the heart or circulation, these are allowed to go without treatment. The one exception is the case of premature beats arising in relation to an acute coronary thrombosis. In these, the premature contractions are sometimes a precursor of a

more serious disorder of rhythm, ventricular tachycardia. It is well to treat them even though the patient is not aware of their presence.

There are several measures employed in the control of premature contractions. Quinidine is by far the most useful, and is effective against all forms, those of auricular, nodal, and ventricular origin. A satisfactory routine dosage for adults is 0.3 Gm. (5 gr.) of quinidine sulfate in the form of a capsule or tablet three times daily. It is an ambulant form of therapy. An intensive cumulative system of dosage is rarely necessary against premature beats because this disorder of rhythm rarely presents an urgent problem. As in all cases, there are marked individual differences in susceptibility to the drug. In some, the abnormal beats may be brought under control by smaller daily doses, while in many, much larger daily doses are necessary. In the typical case in which the daily dose of 1 Gm. (15 gr.) is adequate, the premature beats will disappear after the first day, or after treatment for a period up to four or five days. During this period, a moderate degree of cumulation takes place resulting in a progressively increasing concentration of the drug to which the heart is exposed. As has been stated in the section on Dosage, the curve of cumulation with a fixed daily dose of quinidine flattens out by the fourth or fifth day, and if by that time the premature beats persist, it is evidence that the daily dosage is too small, and that the abnormal rhythm is likely to persist, no matter how long beyond that point the same daily dose is continued. The dose is then increased to 1.3 Gm. (20 gr.) daily (5 gr. every four hours) for four or five days, and in this manner, the increase in daily dose is continued to 25 or 30 gr. or more, until a dosage level is reached which is effective in controlling the premature contractions. That dosage is continued indefinitely for purposes of maintenance. It may

be interrupted for a few days from time to time, in order to learn whether there is any further need for the drug, for in the course of time changes take place in the patient or the heart which eliminate the cause of the premature beats, and thus remove the need for the further use of the drug.



Sinus Tachycardia

SINUS tachycardia is the most common form of rapid heart action. The pacemaker is the sino-auricular node, the mechanism which drives the normal heart. The rapid heart action of exercise, fever, infections, nervousness, and Graves' disease is usually due to a speeding up of the rate of the sinus node, or sinus tachycardia. The rhythm is usually regular and the rate varies widely. This type of acceleration of the heart is usually the *result of inhibition of vagal tone similar to the result of* varying doses of atropine, although under conditions of extreme stress when the rate rises to 150 a minute or more, stimulation of the accelerator (sympathetic) nerves to the heart may be involved.

The control of sinus tachycardia is brought about only by the removal of the cause. For example, the rapid heart rate of fever slows when aspirin lowers the temperature, the rapid heart rate of pneumonia slows when penicillin

checks the infection, the rapid heart rate of Graves' disease slows when iodine or propylthiouracil lowers the metabolic rate. There are no drugs which are useful in the control of sinus tachycardia by direct stimulation of the vagus center or direct depression of the sino-auricular node.

Quinidine is sometimes used in sinus tachycardia to slow the heart, but it is rarely, if ever, sufficiently effective. There is the experimental observation that quinidine depresses the sino-auricular node, and that such an action occurs in man is evident from the occasional instance of severe poisoning which results in sinus arrest. Slowing of a rapid sinus rhythm, short of complete arrest of sinus activity, might be expected, but in actual trial this result is extremely rare. In advanced heart disease, quinidine occasionally leads to sinus bradycardia with rates of 40 or 50 a minute, but in the common conditions associated with sinus tachycardia such as physical exertion, fever, Graves' disease, organic heart disease, and heart failure, there is no conspicuous slowing of the heart by quinidine after even very large therapeutic doses. This may, in part, be due to the well-established fact that the normal sinus pacemaker of the heart is not as sensitive to quinidine as ectopic pacemakers, and in part to the fact that large doses of quinidine block the vagus in the heart. This release of the sinus node from vagal control would mask moderate slowing which might result from direct depressant action on the sinus node.

11

Paroxysmal Auricular Tachycardia

AURICULAR tachycardia is a term applied to a rapid heart action due to an ectopic focus in the auricle. The attack comes on abruptly and terminates abruptly. The rhythm is regular. The rate is very rapid, about 180 a minute or more. In rare cases, the rate is much slower and in occasional cases, much faster. The rate tends to be fixed and shows little tendency to fluctuate with rest or physical exertion. I had under care a streetcar conductor who had had a successful thyroidectomy for Graves' disease, but who during his work was subject to frequent attacks of auricular tachycardia with a rate of 270 a minute. In him these caused negligible symptoms. There are cases in which this kind of rhythm persists for years with occasional interruption by a normal sinus rhythm, but these are extremely rare. I have seen only one such case in twenty-five years. The common variety is paroxysmal. Here the patient is suddenly seized with severe palpitation, a sense of throbbing in the neck and chest. There may be a sense of light-headedness or faintness. In young individuals, the attack may cause no serious symptoms. Aside from the sense of rapid heart action, pallor, and attending apprehension, the attacks come and go uneventfully. On the other hand, in elderly individuals, or in those with coronary disease, or advanced hypertensive

disease, the attacks may result in anginal pain, or heart failure with pulmonary edema. The duration of attacks varies greatly, from a few seconds to many hours, days, or even months. The attacks are not linked to any particular form of heart disease. A large proportion of them are seen in patients who have no organic disease. They sometimes occur during emotional upsets, after anesthesia, and in acute infections. In those with the more rapid rates, the stroke volume is so small that the radial pulse, and the blood pressure measured in the usual indirect manner, disappear.

The mechanism is an irritable focus in the auricular muscle with an exceptional degree of rhythmicity. This focus is extremely sensitive to the cholinergic substance, as seen from the fact that it may be suppressed by carotid sinus pressure and other devices which are known to exert vagal stimulation, mecholyl, and drugs which excite the vomiting mechanism, such as syrup of ipecac or apomorphine. Digitalis is very effective in suppressing these abnormal pacemakers in the auricle.

Quinidine is highly effective in terminating a paroxysm of auricular tachycardia. Many years ago, Otto and I studied a patient subject to spontaneous paroxysms of auricular tachycardia in whom the ectopic rhythm could be precipitated at will by a dose of epinephrine. We happened to have used quinine in this case, and by means of this drug, we were able to terminate and prevent these attacks. The mechanism of the action here has not been established with certainty. The vagal blocking action of quinidine would tend to prolong refractory time in the auricle, but it is probable that the main action is directly on the muscle to prolong refractory time. The mechanism may be similar to that described in the section on Actions. There attention was called to an experimental method for

studying quinidine-like actions of drugs. The method, using the isolated auricle of the rabbit, involves a condition essentially similar to that prevailing in auricular tachycardia. In the case of the rabbit experiment, the auricle, when driven by an electrical shock at the maximum rate at which each stimulus evokes a response before quinidine, shows dropped responses after quinidine, as the result of increased refractoriness. In the clinical paroxysm of auricular tachycardia, if such a state is induced by suitable doses of quinidine, a properly placed discharge from the sinus would enhance the refractoriness sufficiently to terminate the ectopic rhythm.

None of the measures employed for the control of paroxysms of auricular tachycardia is uniformly successful. There are cases which respond best to one method, and some which respond best to another. The incidence of success with quinidine is not known. Many of the failures are undoubtedly due to inadequate dosage. There is the tendency, to which I have referred, to employ a rigid system of dosage, which naturally results in insufficient doses in many cases. I am inclined to believe that a high proportion of cases of paroxysmal auricular tachycardia can be brought under control by adequate doses of quinidine.

Since paroxysmal auricular tachycardia shows a marked tendency to recurrence, most patients present two therapeutic problems, one, to abolish an attack, and the other, to prevent recurrences. In the majority of cases, the routine of 0.4 Gm. (6 gr.) every two to three hours should suffice to terminate an attack. As the intensity of the drug action increases, the rate may show some tendency to slow, but more often the effect on the pacemaker is all-or-none, and one is not likely to observe a progressive slowing of the ectopic rhythm. The abnormal pacemaker usually continues to discharge at whatever rate it had before the drug, until

enough of the drug accumulates in the heart to inactivate the irritable focus completely, when it abruptly ceases to function and the normal sinus pacemaker takes over the task of driving the heart.

The vagal blocking action of quinidine may be a source of misinterpretation. At the same time that quinidine is acting on the auricular muscle, it may also be acting to block vagal control of the sinus node. The result is that when the abnormal focus ceases to function, it may be a rapid sinus node which takes over. In a specific case, for example, the course of events may be as follows: A patient with a paroxysm of auricular tachycardia has a heart rate of 180 a minute; he receives 0.4 Gm. (6 gr.) of quinidine every two to three hours; after the sixth or seventh dose, the heart rate may be found to be 130 a minute. This may be erroneously taken to be a slowing of the ectopic rhythm, whereas in fact, it may represent a complete suppression of the ectopic pacemaker with the normal sinus node in command of the heart. The rapid rate of 130 is, in this case, due to the vagal blocking action of quinidine. It is well to remember this fact, for it is at this point that quinidine should be discontinued. If more quinidine is given, either the rate will remain at 130, or it may go higher by reason of greater blocking of the vagus. If quinidine is discontinued, the rate of 130 will gradually slow as the drug is excreted, and within eight hours or so the normal rate of 70 or 80 a minute will return. The actual rates will differ from case to case. What must be *borne in mind are the general features of this* mechanism: If in the course of the treatment of a paroxysm of auricular tachycardia, one becomes aware of a substantial slowing of the heart rate, even though it is still quite rapid, one may suspect that the therapeutic objective has already been attained—the ectopic focus has

already been suppressed and the normal sinus pacemaker is operating in its place. There are exceptions. If there is doubt, an electrocardiogram taken at this time is usually decisive.

So much for the problem of abolishing a paroxysm of auricular tachycardia. We now come to the problem of preventing its recurrence. The routine of 0.3 Gm. (5 gr.) three times daily (at intervals of about six hours) is a satisfactory starting point. This is essentially a noncumulative system of dosage; the concentration of the drug in the blood and the heart will vary considerably during the day, but there is apt to be only little cumulation from day to day, and after five days, no further cumulation takes place, as described in the section on Dosage. This daily dose may, therefore, be continued indefinitely. If an attack occurs, showing that the dosage level is insufficient, it is well to abolish it by the intensive dosage system described above, and then resume maintenance with 4 doses of 0.3 Gm. (5 gr.) daily (one dose every four hours). If an attack occurs again, the procedure is repeated to abolish it, and then the plan of 5 doses of 0.3 Gm. (5 gr.) daily is continued as the maintenance system. In this way, the maintenance dosage is increased until a level is reached which suffices to prevent recurrence of attacks. It is not uncommon to discover that the dosage level necessary to prevent attacks is as high as, and sometimes higher than, that needed to abolish the attack. The reasons for this have been discussed in the section on Dosage.

The intensive dosage plan for the abolition of an attack should be applied with the patient under close observation and at rest. The chief reason is the fact that when the rapid auricular ectopic rhythm is brought to an abrupt end, the heart may pause before the sinus pacemaker revives and takes over. The interval of cardiac arrest is of varying

duration. It is usually a matter of a few seconds, but there are rare instances in which fifteen seconds or longer may elapse, before the normal rhythm is resumed, and in that period faintness or syncope may occur.

It should not be assumed that all cases of paroxysmal auricular tachycardia should be placed on a maintenance regimen of quinidine. If it is the first attack, it is wise to discontinue the quinidine after the seizure has subsided. It may well be that the particular patient will never have another attack. Such is often the case when the attack is brought on by an acute coronary thrombosis, or some acute infection. If months elapse between attacks, the patient may do better treating each attack than attempting to prevent them by a regimen of treatment which requires the uninterrupted use of quinidine several times daily for many months. There is no lasting effect of quinidine and the patient accumulates no credit for its use during the months in which no attack would have occurred without the drug. It is often a source of great disappointment to the patient who has been faithfully carrying out the order to take 4 or 5 capsules of medicine a day for months, to find himself in an attack on the one day in which, for one reason or another, there was a lapse of one or two doses. The maintenance system of treatment is particularly applicable to patients in whom attacks are frequent, several times a day to once a week or so.

Only the oral route has been considered in relation to paroxysmal auricular tachycardia. The method and dangers of the intravenous use of quinidine are discussed in another section. While an intravenous dose of quinidine may terminate a paroxysm almost at once, auricular tachycardia is not often sufficiently urgent a problem to justify the risk of its treatment by the intravenous route.

12

Nodal Tachycardia

THE mechanism of nodal tachycardia is essentially the same as that of auricular tachycardia. It is a paroxysmal form of ectopic rhythm. The abnormal focus of the rapid pacemaker resides in the A-V node. Its clinical features and treatment are the same as those of auricular tachycardia. It is much more resistant than auricular tachycardia to all measures of treatment.

13

Auricular Flutter

AURICULAR flutter is a disorder of cardiac rhythm of short duration in the vast majority of cases. While there are a few patients in whom it is chronic or permanent, in the vast majority it comes in a single attack, or takes on the form of recurrent paroxysms.

Unlike paroxysmal auricular tachycardia, which often comes and goes in attacks of varying duration for periods of many years, unrelated to any specific event or experience

in the patient's life, a paroxysm of auricular flutter is more apt to be linked to some particular occurrence, such as an acute coronary thrombosis, reactivation of rheumatic carditis, an acute infection, and the like. If a careful search is made, one is more likely to find some acute precipitating cause for the attack of auricular flutter than is the case in paroxysmal auricular tachycardia.

Clinically, the most common form of auricular flutter presents features indistinguishable from a paroxysm of auricular tachycardia. The patient is suddenly seized with a sense of extremely rapidly beating heart, usually regular and with a rate of about 160 or 170 a minute. It is rarely much faster than that, and if the rate is nearer 200 a minute, it is more likely to be a paroxysm of auricular tachycardia. Also, the rate is fixed and does not fluctuate appreciably with rest or exercise. In its typical form auricular flutter differs from auricular tachycardia in its response to carotid sinus pressure, or equivalent measures. Here, when carotid pressure produces an effect, it is not that of terminating the abnormal rhythm, but of slowing the ventricular rate, reducing it to one-half the previous rate, or rendering the pulse or ventricular rhythm slower and irregular. In some instances, it causes complete ventricular arrest. The changes are always fleeting, and the original rhythm returns even when the carotid pressure is continued. These responses may be recorded in the electrocardiogram, and they are helpful in arriving at a diagnosis.

The mechanism of auricular flutter is different from that of auricular tachycardia. In the most prevalent view, the pacemaker in auricular flutter is believed to be a circus movement in a ring of muscle between the superior and inferior vena cava. A continuous wave of excitation develops in this area, usually at a rate of about 350 a minute. These flutter waves may be counted in the electrocardiogram. The

A-V conducting mechanism is too refractory to allow such rapid impulses to pass down to the ventricles. The usual result is a 2:1 block, the ventricular rate being only one-half that of the auricle. The patient therefore presents a heart rate or pulse rate of about 170. In some cases, the refractoriness of the A-V conducting system is irregular, and this gives rise to a rapid and irregular heart rate or pulse rate.

Unlike auricular tachycardia, for the control of which any one of a large number of measures are available, there are only two which are effective in abolishing the abnormal pacemaker of auricular flutter: digitalis and quinidine. Some patients respond only to digitalis, others only to quinidine, while in still others both agents prove equally effective. In many cases there is no basis for a choice in advance. It is preferable to try digitalis in the patient who also has congestive failure. Otherwise, it is usually advisable to try quinidine first. The advantage of trying quinidine first lies in the fact that it is rapidly eliminated and, should maximum doses prove ineffectual, one may proceed with digitalization after an interval of twelve or twenty-four hours. As is pointed out in another section, there is danger in the combined use of massive doses of quinidine and digitalis. When one has used digitalis first, and it has proved ineffectual, unless it is one of the rapidly eliminated digitalis glycosides, it is well to wait several days to allow for a considerable degree of recovery from the digitalis before one turns to quinidine in the endeavor to abolish the attack of flutter.

The plans of dosage of quinidine both for the abolition of an attack and for the prevention of recurrences are similar to those already described for auricular tachycardia. In the usual case, to abolish an attack, one begins with 0.4 Gm. (6 gr.) and repeats the dose every two to three hours.

In many cases, all that is seen is a rapid heart rate of,

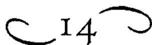
let us say, 160 a minute at the beginning, and after several doses, a normal rhythm with a rate of 70 or 80 a minute in its place. If one follows the course more closely, however, one is often able to detect the various stages in the process of abolishing the flutter and restoring a normal rhythm. As the blood concentration of quinidine rises with the increasing doses, the ventricular rate and the rate of the flutter in the auricles, as seen in the electrocardiogram, begin to slow. For example, in a particular case, the rate of the auricle may be 320, and of the ventricle 160 at the beginning; after several doses of the drug, the rate of the auricle may decline to 300, and, of the ventricle, to 150; as the doses are continued, the rate of the auricle may decline to 250, and, of the ventricle, to 125. Up to this time, there has been considerable slowing of the heart and pulse rate, but the mechanism is still that of auricular flutter with a 2:1 block. After additional doses, the rate of the auricle may decline to 200, and at this point the rate of the ventricle or pulse, instead of falling further, suddenly rises to 200, to equal the rate of the auricle. Now further doses may produce some further slowing of both the auricle and ventricle, to 180 or even 160 a minute, when suddenly the heart stops, usually for only a few seconds, and then resumes its beat with a normal rhythm and rate of 70 or 80 a minute.

These fluctuations in the heart rate and pulse rate are confusing and incomprehensible unless one bears in mind the mechanism at work. At the beginning of the treatment in auricular flutter, the auricle is discharging at 320 a minute and the ventricle is responding to only 160 of these impulses because of the refractoriness of the A-V node. Quinidine slows the speed of the circus movement in the auricle, and this results in a slowing of the ventricle as long as the 2 1 block persists. When, however, the rate

of the auricle is reduced to about 200 a minute, the 2:1 block disappears, since the node is rarely refractory to a rate of 200, and at this point the ventricle begins to respond to all the auricular impulses. With the establishment of the 1:1 rhythm the heart rate suddenly rises. The second phase of cardiac slowing then begins as the increasing action of quinidine produces further slowing of the circus movement in the auricle in the presence of a 1.1 rhythm. The slowing of the circus movement tends to perpetuate the flutter, but at the same time that quinidine is slowing the rate of the circus movement, it is also increasing the refractory time of the auricular muscle, and when the refractory time is sufficiently long, the circus movement comes to an abrupt end. This usually takes place when enough quinidine action has developed in the auricle to slow the rate of the circus movement to about 180 a minute. The abrupt cessation of impulses from the auricle in flutter leaves the heart without a pacemaker; the entire heart stops beating, and after an interval of a few seconds, the sinoauricular node resumes its rhythmic discharge and takes over the function of driving the heart at a normal rate and rhythm.

There are numerous variants of this pattern, arising from the fact that quinidine exerts several actions at the same time; these have been described in the section on the Actions of Quinidine. The drug may fail to abolish the flutter because toxic effects arise before sufficient prolongation of refractory time is present. Disturbing acceleration of the heart may occur because marked vagal depression may lift the 2:1 A-V block when the rate of the flutter in the auricle is still very rapid. An irregular ventricular rhythm may appear because of a direct action of quinidine on the A-V node giving rise to varying A-V conduction. The failure of quinidine to restore a normal rhythm in

auricular flutter is sometimes due to an unfavorable balance between the two opposing actions on the auricle: that of prolonging refractory time which tends to abolish the circus movement, and that of slowing conduction which promotes the continuation of the circus movement. When these two actions happen to be improperly balanced in a particular case, quinidine may slow the rate of the auricle and ventricle, but the restoration of a normal rhythm will fail to take place after even toxic doses. If one is encountering difficulties during the use of quinidine in the attempt to abolish auricular flutter and restore a normal rhythm—if, for example, the heart rate has slowed moderately from the original level of about 160 to about 120 a minute, after 2 to 3 Gm. (30 to 45 gr.) have been administered, it is well to check the situation by means of the electrocardiogram. It may well be, in such a case, that the normal sinus rhythm has already been restored, but is maintained rapid by the blocking action of quinidine on the vagus.



Auricular Fibrillation

IT WAS the effect of quinine in auricular fibrillation which first directed attention to the value of the cinchona alkaloids in disorders of cardiac rhythm. The discovery was made by a patient of Wenckebach's, who was suffering with an extremely irregular

heart, and who was in need of taking quinine periodically as a protective against malaria. He observed that during those periods, his heart became regular. Wenckebach looked into the matter further and found that quinine was effective in abolishing auricular fibrillation. A few years later, Frey tested several members of the cinchona group, and observed that quinidine was more effective than quinine for this purpose. The early reports were stirring, for they indicated a new cure for a form of cardiac disorder which afflicts about 20 per cent of all patients with heart disease. The extensive research and experience of the past thirty years have gone a long way in crystallizing the place of quinidine in auricular fibrillation, its utility, limitations, and dangers.

There are two general classes of patients, those with the chronic form, and those with the paroxysmal form of auricular fibrillation.

Shortly after the discovery of the effect of quinidine in this type of ectopic rhythm, the drug was widely applied to patients with the persistent or chronic form of auricular fibrillation. Many of these patients had long-standing rheumatic heart disease, in many the heart had become very large, and in many there was heart failure. Quinidine proved successful in restoring the normal rhythm in a high proportion of these cases, and in a few the cardiac and circulatory status improved. However, in most of them the results were not particularly satisfactory. While the rhythm had become regular, the rate was now often rapid and could not be readily slowed by digitalis, unlike the case when the patient was maintained in auricular fibrillation. In some, even though a normal rate and rhythm had been restored, the patient seemed to be no better off, since the heart failure persisted and needed to be treated with digitalis. In some, it was found extremely difficult to maintain the normal

rhythm, and the fibrillation returned even though large doses of quinidine were continued. In the course of time, a few disasters were encountered, sudden deaths or discharge of emboli from thrombi which had formed in the auricles during the long period of fibrillation. These experiences led to a re-evaluation of the indications for quinidine in auricular fibrillation. The result is that its use in long-standing auricular fibrillation has for the most part been abandoned.

It is the paroxysmal form which provides the chief indication for the use of quinidine in auricular fibrillation. Attacks of auricular fibrillation often appear in patients without evidence of organic heart disease. By far the larger proportion of cases, however, involve a heart that is the seat of organic disease, arteriosclerotic, hypertensive, rheumatic, and other forms. As in other paroxysmal forms of ectopic tachycardias, the attacks come on abruptly and terminate abruptly. The heart rate is usually rapid, 120 or more a minute, the rhythm is totally irregular, and not all beats come through to the radial artery, giving rise to a pulse deficit. Aside from the sensation of rapid and irregular pounding in the chest, some of these attacks give rise to anginal pain, heart failure, or pulmonary edema. Occasionally, the paroxysm of auricular fibrillation gives rise to such severe substernal pain that there is for a time uncertainty as to whether it is an attack of coronary thrombosis resulting in auricular fibrillation or whether the ectopic rhythm is causing symptoms of coronary insufficiency, a question which is decided by the frequency of the attacks and the sequence of events. The duration of the attacks varies greatly from case to case, and as, in other paroxysmal disorders of ectopic rhythm, the attacks may last from a few seconds to hours, days, or weeks, unless measures are taken to control them.

In the use of quinidine for auricular fibrillation, there are again two problems, to abolish the attacks and to prevent recurrence. With a patient in the midst of an attack of auricular fibrillation, the question as to whether quinidine should be used is to be preceded by the question as to whether it is wise to abolish the fibrillation in this particular case.

The answer to the second question is the answer to the first, for there are no agents in common use other than quinidine or its related cinchona alkaloids which possess any substantial power to abolish auricular fibrillation. There are some cases in which acute failure causes fibrillation of the auricles and the relief of the failure by digitalis restores the normal rhythm, but more often the relation of events is reversed: The attack of auricular fibrillation precipitates heart failure, and digitalis increases the tendency of auricular fibrillation to persist.

The judgment as to the wisdom of terminating the auricular fibrillation depends on several factors. The first question is, how long has it persisted? There is some indication that intramural thrombi are more apt to form in patients with auricular fibrillation than in those with normal sinus rhythm, due to the stasis of blood in the fibrillating auricles, because these auricles do not contract as a whole. How long it takes for such thrombi to form is unknown. In general, it is considered unwise to attempt to abolish the fibrillation after it has persisted some weeks. The duration of the fibrillation is not the only source of danger. The presence of a very narrow mitral valve with marked enlargement of the heart, particularly enlargement of the left auricle, provides a special source of risk, for such cases are especially prone to develop intramural thrombi within the auricles. There are other patients in whom the abolition of auricular fibrillation is attended

by a special risk, namely, those who are known to have had emboli at one time or another, and those with congestive failure, who are especially prone to form thrombi. The hazard in all of these cases appears to lie in the sudden contraction of the auricles when the fibrillation ceases, resulting in the discharge of an embolus. An example may help to understand the nature of such disasters: A woman, 40 years of age, had a long-standing rheumatic heart disease with mitral stenosis and insufficiency. There was moderate enlargement of the heart and some enlargement of the left auricle. There was no heart failure. She developed an attack of auricular fibrillation. The irregular pounding of the heart was very disturbing to her. It was allowed to continue for about three weeks in the hope that it would terminate spontaneously. The patient became very unhappy about this new development, since the heart disease in the past had caused her virtually no discomfort. The decision was reached to abolish the fibrillation with quinidine. She received 0.3 Gm. (5 gr.) of quinidine three times daily. She proved to be quite sensitive, and three hours after the last dose on the first day, a normal rhythm was restored. Eight hours later, she developed a severe pain in the right leg with pallor and coldness indicating an embolus. This cleared in about thirty minutes. Two hours later, she developed a hemiplegia due to an embolus in the left hemisphere. This also cleared in a few hours. Four hours later, she developed another embolus to the brain which resulted in coma, and two days after the normal rhythm was restored, the patient expired. This could have been a coincidence, but there are now a sufficient number of analogous experiences which leave little doubt that the restoration of a normal rhythm after fibrillation has continued for some time may result in disaster. It is good fortune that such occurrences are rare. Against these misfortunes,

there are the cases in which the restoration of a normal rhythm puts an end to showers of emboli which some patients experience during the course of chronic auricular fibrillation, presumably as the result of improved circulation through the auricular chamber diminishing the tendency to intramural thrombosis.

That the restoration of a normal rhythm in a patient with auricular fibrillation may cause the discharge of emboli is not universally accepted. It is argued that emboli from the heart are very frequent even when the rhythm is normal, and there is no convincing proof that they are *more frequent in auricular fibrillation. There is, however,* the point that intramural thrombi formed while the auricle is fibrillating may not be sufficiently adherent to the wall to keep them in place when the auricle suddenly begins to contract with vigor, and that may explain the observation that occasionally embolization takes place shortly after the normal rhythm is restored.

Emphasis should be placed on the fact that these accidents occurring after quinidine are not due to any inherent toxic effect of the drug, but are due to the restoration of a normal rhythm; they would be expected to occur after any other drug which had the power to abolish auricular fibrillation. I mention this point because of an experience in which a patient with acute coronary thrombosis and auricular fibrillation developed a hemiplegia within a few minutes after quinidine had restored the normal rhythm. When the fibrillation returned, the physician again resorted to quinidine, but now, because of the original accident, in only very small doses, much too small to restore a normal rhythm. This is clearly a misunderstanding of the issues, for the accident was not due to the dose of the drug, but to the fact that a normal rhythm was established. The result was that the patient continued to receive quinidine

in ineffectual doses and continued to exhibit fibrillation of the auricles. In this case it is worth noting that a subsequent course of large doses of quinidine (0.6 Gm. every three hours) restored a normal rhythm uneventfully. It may also be noted that, if the hemiplegia was due to restoration of the normal rhythm the first time, this case indicates that a repetition of the treatment at a subsequent time may, in some cases, be carried out without untoward results.

From what has already been stated, it is clear that much remains that is unknown about the conditions which predispose to embolic accidents when auricular fibrillation is terminated. There are large numbers of patients with auricular fibrillation which has lasted for years, in whom quinidine restored a normal rhythm uneventfully. How long it takes for the thrombus to form undoubtedly varies greatly from case to case. The character of the thrombus which may lead to an embolus seems to be determined by more factors than its age. There is little doubt that quinidine is credited with accidents which are purely coincidental. Again, there is the good fortune that these accidents are rare, and if the restoration of a normal rhythm is attempted hours after the attack comes on, the danger is not great. Those patients who have had previous attacks which terminated spontaneously without emboli, are particularly favorable, for in them, the action of quinidine amounts to nothing more than terminating the attack sooner, and thereby reducing the danger of embolization which might occur in the event that a particular attack of fibrillation were to come to an end spontaneously after it had persisted a longer period of time.

A course of heparin or dicumarol therapy preparatory to quinidine for the restoration of a normal rhythm might reduce the risk of embolus in auricular fibrillation which has persisted for some time. Although there is no proof

of their value in such cases, there is ample evidence that these anticoagulants inhibit thrombus formation and may diminish the hazard of the fresh thrombus.

The mechanism of auricular fibrillation is most commonly believed to be that of a complex circus movement in the muscle of the auricles. It produces impulses, usually at the rate of about 450 or 500 a minute. Most of these are blocked at the A-V node so that the ventricular response is much slower. The ventricle usually beats at about 120 a minute, and the rhythm is irregular. As the intensity of the quinidine action is increased by repeated doses, the speed of the circus movement in the auricle is reduced. This should have the effect of reducing the speed of the ventricle also, but, as already stated, it often happens, and especially after fairly large doses, that quinidine blocks the vagus and reduces the degree of A-V block, so that the rate of the ventricle rises while that of the fibrillating auricles falls. When the speed of the fibrillating auricles is reduced to about 350 or 300 a minute, the mechanism changes from auricular fibrillation to auricular flutter. The electrocardiogram shows a change from the very rapid and irregular deflections of fibrillation to the slower and regular deflections of flutter. From this point on, the increasing intensity of quinidine action gives rise to a series of events similar to those described in the section on Auricular Flutter.

As in other disorders of rhythm, a wide variety of patterns of response to quinidine in auricular fibrillation may occur by reason of the various actions of the drug occurring simultaneously. They can only be understood if these actions are kept in mind. They sometimes determine the change in the initial plan of treatment. For example, a man, age 53, with arteriosclerotic heart disease, developed an attack of auricular fibrillation with an apex rate of 172 a minute. The patient was digitalized and the apex rate

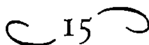
was reduced to about 80 a minute. An attempt was then made to abolish the ectopic rhythm by means of 0.4 Gm. (6 gr.) quinidine every three hours. After 10 such doses or a total of 4 Gm. in twenty-four hours, the patient suddenly developed an unfavorable reaction; there was a cold clammy sweat, extreme cyanosis, and pulmonary rales. The rhythm had changed from a slow and irregular beat at the apex to a regular rhythm with a rate of 180 a minute. An electrocardiogram taken at this point showed a supraventricular tachycardia, perfectly regular, and prolonged intraventricular conduction (QRS time of 0.12 second). The rhythm was that of auricular flutter. Since the original electrocardiogram of the auricular fibrillation with the ventricular rate of 172 a minute showed normal intraventricular conduction (QRS time of 0.06–0.08 second), it was assumed that the prolongation of intraventricular conduction was not the result of fatigue by the rapid rate, but of a toxic action of the quinidine (see section on Toxic Actions). Here was a case, therefore, in which the expected series of changes was taking place after quinidine in auricular fibrillation, namely, passage from fibrillation to flutter, but in this particular individual so much quinidine action on intraventricular conduction had developed by the time the flutter appeared that the electrocardiogram took on the aspect of ventricular tachycardia. In view of this, it was deemed unwise to continue the attempt to restore the normal rhythm by the intensification of quinidine action. The quinidine was discontinued and twenty-four hours later the flutter came to an abrupt end; a normal sinus rhythm took its place. In another section it has been stated that quinidine exerts two opposing actions on the auricular muscle: one, to prolong refractory time which tends to abolish flutter or fibrillation and the other, to slow conduction which tends to promote their

continuance. In the case cited above, the action of slowing conduction was dominant with the result that the flutter became fixed.

Another case may be cited in which the various actions of quinidine on the heart complicated the problem of controlling auricular fibrillation. This patient, 44 years of age, had arteriosclerotic and hypertensive heart disease. He was subject to paroxysms of auricular flutter and fibrillation, sometimes one and sometimes the other. There were several attacks a month over a period of about four years. He was completely incapacitated by these attacks because some of them produced syncope. Without treatment, the heart rate during a seizure was about 150 a minute. There was no appreciable influence on the attacks until the dosage of quinidine was increased to 2 Gm. (30 gr.) daily. Now the attacks still occurred but the disturbance they produced was negligible because the heart rate during a paroxysm was only between 80 and 90 a minute. The disturbance was so slight that it became difficult for him to know when the rhythm was normal or abnormal. This, therefore, is an instance in which quinidine behaved more like digitalis in a patient with auricular fibrillation. It allowed it to continue but induced so much A-V block as to reduce the heart rate to a tolerable level. Still another situation arose in this patient; the quinidine, at one level of dosage, provided a more favorable state for auricular fibrillation. Whereas before the quinidine, attacks lasted only a few hours, and the longest attack during a four-year period lasted less than three days, during the use of 2.7 Gm. (40 gr.) quinidine daily, he not only developed more frequent attacks, but had an attack of auricular fibrillation with a slow ventricular rate which lasted a period of about fourteen days. This is evidence of a predominant action of quinidine on the conduction rate of the circus movement

in the auricle; by slowing the conduction rate without significant increase in the refractory time, the development of the circus movement is favored, and it becomes more stable. This is the action which sometimes fixes auricular flutter and makes it impossible to terminate an attack of auricular flutter or fibrillation with quinidine. When, in this patient, the dose was increased to 4 Gm. (60 gr.) daily, enough prolongation of refractory time took place to terminate the fibrillation and restore a normal sinus rhythm which continued during a period of several years as long as that daily dosage was taken.

The most favorable dosage plans for terminating a paroxysm of auricular fibrillation and preventing recurrences are similar to those for auricular flutter, and are described in the section dealing with flutter.



Ventricular Tachycardia

VENTRICULAR tachycardia is one of the less common forms of ectopic rhythms. Its occurrence in individuals with an otherwise normal heart is rare. It is usually associated with advanced grades of heart disease, more often hypertensive and arteriosclerotic disease. It most commonly presents itself as a problem in patients who have suffered an attack of coronary thrombosis. It is never a long-lasting tachycardia. In a small

number, it takes on a paroxysmal character; attacks come and go over a period of years. It does not, however, frequently behave in this way, and when a patient complains of frequent attacks of rapid heart action over periods of years, paroxysmal ventricular tachycardia is least likely to be the correct diagnosis. The story in most cases is likely to involve a single attack or a series of attacks over short periods of time, most often in relation to a serious cardiac upset, especially an acute coronary thrombosis. In all of these respects it differs from ectopic auricular tachycardia.

The onset is abrupt, so also the spontaneous termination. The rate varies greatly from case to case. It is usually rapid, in most cases in the range of 150 to 250 a minute. There is negligible fluctuation in rate with rest or exertion. The rhythm is usually regular. The mechanism is that of a series of premature ventricular contractions. The series may be of varying length, anywhere from 2 or 3 beats in succession, to an uninterrupted series lasting days. There is no question of the diagnosis in the case of a long series, but there is no sharp line of division, and the question as to how many beats in succession there need be to label it ventricular tachycardia remains unsettled. It is customary to refer to a series of 2 or 3 premature ventricular beats in succession as a precursor of ventricular tachycardia, and a large number in a row, as a short run of ventricular tachycardia. These appear to involve a type of increase in irritability or rhythmicity of the heart which differs from that in the case of isolated premature ventricular contractions, which is very common in those with and without heart disease. It is often stated that the rhythm of ventricular tachycardia may be grossly irregular. That is, indeed, sometimes the case, but, in those patients with irregular rhythm labeled ventricular tachycardia, I have often discovered an error in the reading of the electrocardio-

gram. The irregular rhythm turned out to be supraventricular ectopic rhythm with bundle branch block, either auricular fibrillation or flutter with bundle branch block.

The electrocardiogram is essential for the diagnosis of ventricular tachycardia. The carotid sinus pressure test is sometimes helpful in excluding ventricular tachycardia which may clinically appear similar to a paroxysm of auricular tachycardia or auricular flutter, all three showing, for example, a regular rhythm with a rate of 170. The origin of the latter two is in the auricle which is supplied with vagal fibers, while that of the former is in the ventricle, not supplied by the vagus. If carotid pressure, therefore, causes a change in the rhythm, ventricular tachycardia is excluded. A negative response is, however, of no help because there are many cases of auricular tachycardia and flutter which also fail to respond to carotid pressure. Another useful point in diagnosis may be mentioned. In many cases of ectopic tachycardia, the activity of the auricles in the form of P-waves or F-waves of the electrocardiogram is masked in the rapidly recurring deflections of the ventricles. If the ventricular deflections show normal conduction (QRS time of less than 0.10 second), a diagnosis of supraventricular tachycardia is made. If the intraventricular conduction is prolonged (QRS time of 0.12 or more), it is either ventricular tachycardia, or supraventricular tachycardia with bundle branch block. If, however, the latter kind of tracing reveals auricular deflections, occurring in a fixed relation to those of the ventricles, it is most likely not ventricular tachycardia but supraventricular tachycardia with a bundle branch block. This is so because it is unlikely that the auricles and ventricles will beat rapidly at identical rates, and do so independently of each other. Since, in such a case, one drives the other, it must be the auricles driving the ventricles, rather than the reverse. Normally, con-

duction takes place in only one direction, from the auricle to the ventricle, not from ventricle to auricle. It is well known that when an electrical stimulus, applied to the auricle, produces a premature auricular contraction, it may be followed by a contraction of the ventricle; a similar stimulus applied to the ventricle causing a premature ventricular beat is not followed by a contraction of the auricle.

The treatment of ventricular tachycardia often presents an urgent problem. The rate is apt to be very rapid, the efficiency of the circulation is markedly impaired, and the blood pressure falls. Congestive failure or peripheral circulatory collapse or both may supervene; the patient develops cold and clammy skin with or without pulmonary edema. Its seriousness does not lie in the fact that the heart is driven by an abnormal pacemaker in the ventricle, for a similarly serious state is sometimes caused by an abnormal focus in the auricle, as in a paroxysm of auricular tachycardia which suddenly begins to drive the heart at 200 a minute or faster. The serious aspect of ventricular tachycardia lies chiefly, if not entirely, in the fact that this type of ectopic tachycardia occurs so commonly in patients with a badly damaged heart or circulation which is unable to bear the sudden stress of the extreme speed and diminished circulatory flow.

Quinidine is the most important agent available for the treatment of ventricular tachycardia. An intravenous injection of procaine, magnesium sulfate, and other drugs have been found effective in some cases, but experience with these agents is limited. The ultimate objective in the treatment of an attack of ventricular tachycardia is to suppress the rapid pacemaker in the ventricle. When that takes place, the ventricle stops beating, and the discharge from the sinus pacemaker in the auricle is conducted down to the ventricle causing it to contract. In this way, the normal rhythm is established. Basically it is a simple problem but in prac-

tice many difficulties may arise, partly due to the nature of quinidine action, and partly due to the state of the heart, and these must be understood in order to comprehend unexpected results and to prevent disasters.

For the restoration of a normal rhythm in a case of ventricular tachycardia, dependence is placed on one action of quinidine, that of depressing the rhythmicity of the idioventricular pacemaker until its rhythmic function comes to an end, and the normal sinus node takes over. For this to take place, certain conditions must prevail in the heart, these being an active S-A node ready to resume rhythmic discharge, an active A-V conducting system ready to deliver the impulse to the ventricle, and a ventricle sufficiently irritable to respond to the impulse. If all of these conditions prevail, a few doses of quinidine abolish the ventricular tachycardia and establish a normal rhythm uneventfully. There are, however, cases in which some of these functions are impaired or suppressed, and then the abrupt abolition of the idioventricular tachycardia gives rise to trouble. The disease of the heart may suppress the auricular pacemaker or produce A-V block. There is experimental evidence that extremely rapid excitation of the ventricle tends to suppress its automaticity, as evidenced by the long delay following cessation of the stimulus in such cases, before the ventricle resumes its beat. The delay may be as long as fifteen seconds or more, giving rise to coma or convulsion. Such effects may also be produced by quinidine, or quinidine may increase the tendency to such changes, which may already be present. Quinidine in large doses also has a tendency to depress myocardial contractility, and in such badly damaged hearts may lead to acute myocardial failure.

It has already been indicated that the abolition of ventricular tachycardia by means of quinidine is a very important and often life-saving measure. It has also been

stated that ventricular tachycardia is rarely a chronic state. It either terminates spontaneously in a short time or is terminated by means of quinidine fairly promptly. Those patients in whom it tends to persist and the drug fails, develop cardiac or circulatory failure and succumb to these in a short period of time.

The foregoing considerations supply the basis for the method and dosage plan which I have used with a fair degree of success, and which I advocate for treatment of the attack of ventricular tachycardia, as a means of insuring satisfactory results in the largest number and with a minimum of danger. In the first stage of this method, one does not aim to abolish the ventricular tachycardia, but only to slow its rate. A rate of 230 a minute fatigues the heart and damages the circulation. The first step is to try to reduce the speed of the heart to a more favorable rate, usually to about 120 or 110 a minute. This may already be a normal sinus rhythm, or still an idioventricular rhythm. There is no evidence that the latter at a rate of 110 is any less favorable to the circulation than a sinus rhythm at 110 a minute. The reason one does not aim to abolish the ventricular tachycardia directly is the fact that one does not know in advance what remains when the idioventricular rhythm is suppressed. One may find arrest of the auricle in which no sinus discharge is produced, or A-V block so that the sinus impulse cannot get through to the ventricle. The result is cardiac standstill which may prove disastrous. It is noteworthy that even such a hazardous state of affairs is not always fatal, and after an unpleasant period of time, the heart resumes a beat from some focus. The period is unpleasant because the patient develops cyanosis, or gray pallor, the respiration becomes labored, the eyes roll up, coma develops, and convulsions may supervene. I have often been thankful that I had resisted the temptation to

continue the drug to the point of suppressing the ventricular tachycardia. In these cases, after several doses of quinidine which had slowed the rate from 220 to about 120 a minute, I examined the electrocardiogram and found the disquieting evidence of ventricular tachycardia at 120 a minute without any signs of auricular activity, or an auricular rhythm faster than that of the ventricle, indicating complete heart block. Had I pressed the treatment further at this point, there is little doubt that the ventricular tachycardia would have vanished, and with it, all rhythm in the ventricle would have vanished.

To treat ventricular tachycardia with the highest incidence of success and lowest chance of disaster, the procedure should be carried out under the constant supervision of the physician and with the aid of the electrocardiogram. To prescribe a dose of quinidine to be taken at certain intervals until the patient feels better or is aware of a change of rhythm is a procedure which can never be justified. The principles are the same, but the details vary from case to case, and in any plan with which one starts alterations are often required by the course of events. One satisfactory type of regimen may be described. An electrocardiogram is taken before therapy, and then a dose of 0.6 Gm. (10 gr.) quinidine is given every three hours. The apex rate is counted before each dose. The count should be precise and recorded, since slowing of rate is the most important guide to the development of quinidine action in these cases. Another electrocardiogram should be examined if the rate shows considerable slowing, to a level of about 140. This may occur in three hours after the first dose, or only after 10 or more doses. At this point, even though the rate is 140 or 130 a minute, the electrocardiogram may show that the ventricular ectopic rhythm has vanished and no further therapy is needed.

If the course of events is different, and the original very rapid rate continues, an electrocardiogram should be taken before each dose after the third. The object is to detect prolongation in the QRS time as indication of impaired intraventricular conduction. This is a toxic effect which rarely occurs with less than 2 Gm. and it is not wise to continue the quinidine if the QRS time has been prolonged by about 50 per cent above the control in the particular patient (QRS of 0.08 to 0.12, or QRS of 0.12 to 0.18 second). With these points in mind, one often finds it possible to continue the quinidine until the heart rate is about 120 or 110 a minute. At this point, the use of quinidine is interrupted, but similar counts of the heart rate are made, and electrocardiograms are taken at the same intervals. Often a normal rhythm may be seen in the next few periods of observation. If not, or if there is evidence of quinidine effects wearing off, as shown by an increasing heart rate, the drug may be resumed with the same dose and interval, or with half the dose (0.3 Gm., or 5 gr.), in the endeavor to maintain the state which prevailed at the time the quinidine was interrupted.

Should this result in intensification of the action so as to terminate the idioventricular rhythm, there is the fact that this is safer when the heart has been beating for some time at 120 than at 240 a minute. This has to do with the fact that the sinus rhythm sometimes fails to take over when the ventricular tachycardia is abolished, and abrupt cessation of a very rapid idioventricular rhythm may leave the rhythmic activity of the ventricle so depressed that a pause long enough to produce a convulsion may ensue before an idioventricular rhythm is resumed. It is not always possible to maintain a check on quinidine action and secure such graded effects as have been described. However, such gradation of effects will frequently occur, if the

above described cumulative dosage system is employed and the general principle I have described is kept in mind: to aim at gradually increasing the intensity of quinidine action until the rapid ventricular rhythm is reduced to a reasonably slow rate of 120 or 110 a minute, then to maintain that level of action until physiologic adjustments restore the normal rhythm.

I have laid emphasis on the importance of closely observing the cardiac mechanism with the electrocardiogram after the rate falls considerably, as from 200 to 140 a minute, even if only one or two doses of 0.6 Gm. have been given. An experience in this regard will help to fix the point. The family physician had a female patient in advanced arteriosclerotic disease who went into circulatory collapse in association with an attack of rapid heart action, 190 a minute, which in the electrocardiogram seemed to be a ventricular tachycardia. He was advised to give 0.6 Gm. (10 gr.) quinidine every two hours and examine the electrocardiogram taken before each dose. This was not a particularly attractive prospect because the first dose was to be given at 10 o'clock on Saturday night. A tracing was taken before the first dose and again before the second dose at 12 midnight, at which time the rate had fallen to 160 a minute. Both tracings were developed and examined at once, and showed ventricular tachycardia. Before the third dose at 2 A.M., the heart rate had declined to 140 a minute. The system of doses and tracings at two-hour intervals was continued throughout the night until 9 o'clock Sunday morning. Since the rate did not fall any further, and tended later to rise to 150 a minute, none but the first two electrocardiograms was developed and examined until the following morning. What they showed was that the failure to examine every tracing before the next dose cost the observer a whole night's sleep; the normal rhythm

was established in the tracing at 2 A.M. before the third dose, when the heart rate was 140 a minute. The rapid rate was due to the vagal depressant action of quinidine to which this patient happened to be unduly sensitive. The increase in rate during the night was due to intensification of this action by the additional doses. The drug should have been discontinued at 2 A.M. just before the third dose. The additional 3 doses were not only unnecessary but probably delayed restoration of the circulation by the marked sinus acceleration. Within twelve hours after the last dose, as the quinidine was excreted, the heart rate declined to 108 a minute, which appeared to be the sinus rate of this patient in failure.

The cumulative system of dosage is the only one applicable to the use of quinidine in an attack of ventricular tachycardia. The single dose of 0.6 Gm. (10 gr.) is rarely sufficient to achieve the therapeutic results. Sometimes, the desired effect appears in two to three hours after the second dose, a total of 1.2 Gm. (20 gr.). There are marked individual variations in sensitivity. Some cases require as much as 5 Gm. (75 gr.) or more by the same dosage plan. The dosage system here described provides its own safety controls, regardless of the total amount. The dosage steps are such that, if the previous quantity given as outlined has caused no toxic effects, the next dosage step will cause no serious toxicity. The appearance of toxic effects, referable either to the heart, head, or gastrointestinal tract, usually calls for cessation of the quinidine therapy.

Thus far only the oral route has been considered. The usual quinidine preparations are too irritant and painful for routine use by intramuscular injection. The intravenous route is sometimes necessary because the patient is too ill to take anything by mouth, or vomiting and diarrhea from local irritation preclude the use of adequate doses. The patient may be *in extremis* and since here time may

be the decisive factor, the intravenous route may be used. This is a heroic measure. The dangers are great, and it should rarely be applied except in very serious situations. A 1 per cent solution of quinidine sulfate may be freshly made by dissolving 0.2 Gm. of the salt in 20 cc. of distilled water. This may be injected slowly, using a 26- or 24-gauge needle on a 20 cc. syringe. Intravenous doses of quinidine injected rapidly are especially hazardous, and have caused death. An intravenous dose as small as 0.2 Gm. injected suddenly may cause an abrupt fall of the blood pressure of 40 or 50 mm. Hg. The procedure is better carried out by two operators, one observing the patient and with the stethoscope listening at the apex, the other making the intravenous injection. As the injection proceeds and the drug begins to act, the blood pressure falls, the respiration deepens and becomes labored, the heart sounds become more distant, and the rate slows. There are cases of ectopic rhythms as some of those encountered in anesthesia and surgery, in which a dose as small as 0.2 Gm. (3 gr.) injected in this manner restores the normal rhythm. In many cases, however, larger amounts are necessary. In these, when the heart rate has slowed by 25 or more beats a minute, or when the heart sounds have become very feeble, the injection is interrupted until the respiratory changes, vasodepression, and enfeebled heart sounds right themselves. This usually takes place in a few minutes. Some slowing of the heart is apt to persist. The procedure is then repeated with further slow injection. The result is a series of cardiac slowings which summate, the intervals between injections allowing for recovery from the toxic effects of high concentrations of quinidine in the blood stream. This is continued until the heart rate is reduced to 120 or thereabouts. Frequent electrocardiograms are helpful guides in this procedure.

16

Ventricular Fibrillation

LITTLE needs to be said of the use of quinidine in ventricular fibrillation. It has already been indicated that quinidine prevents ventricular fibrillation. Such prophylaxis may be especially important in cardiac and pulmonary surgery, or in general anesthesia, especially with cyclopropane. However, with the possible exception of a surgical case in which the heart is exposed and accessible to massage, one is not likely to encounter ventricular fibrillation in which much of value may be anticipated from treatment. There are a few patients who have recovered from an attack, and there are a few of the paroxysmal variety. Ventricular fibrillation is probably not uncommon in coronary thrombosis and heart block, and although most cases are rapidly fatal before treatment can be applied, some cases of Stokes-Adams disease in which periods of syncope are due to fleeting ventricular fibrillation may be brought under control by quinidine. Usually, however, as soon as this mechanism is established, the ventricle ceases to contract as a whole, the blood pressure promptly falls to zero, and death ensues. It is an occasional cause of death in digitalis poisoning, and a cause of death which occurs almost immediately after an intravenous injection of a mercurial diuretic in especially susceptible individuals. The diagnosis often remains uncertain even with the electrocardiogram. In animal experiments with the chest open, the simultaneous inspection of the heart, the recording of

the blood pressure, and the recording of the electrocardiogram often show the difficulty of distinguishing ventricular fibrillation from ventricular tachycardia. The onset of ventricular tachycardia with visible contractions of the ventricles and sustained blood pressure may be promptly followed by visible arrest of the ventricle with the quivering of the walls, and abrupt fall of the blood pressure to zero. The electrocardiograms during the two phases may be indistinguishable, sometimes both showing regular deflections and other times bizarre and irregular ones.

With the electrocardiogram alone as a guide, as is the case in clinical situations, the phase of ventricular tachycardia might be labeled fibrillation, or *vice versa*. I have seen only one case of so-called paroxysmal ventricular fibrillation. Listening at the apex and recording the electrocardiogram simultaneously, I heard the sudden onset of a tachycardia too rapid to count. The presence of audible sounds indicated ventricular tachycardia. Within less than one minute, the sounds disappeared, the patient flushed and then paled, the respiration became labored, the eyes rolled up, and a convulsion ensued. This phase suggested ventricular fibrillation, although the changes might have been due to the impaired blood flow as the result of the rapid heart rate. The distinction might have been made by direct inspection of the heart, if that had been possible. The electrocardiogram was of no help. In both phases there was an irregular and bizarre idioventricular rhythm with a rate of approximately 260 a minute. Within about three minutes a more favorable and slower rhythm reappeared and the patient recovered. She had several such attacks over a period of two years. Quinidine in the doses used seemed to be of no benefit in this case.

17

Disorders of Cardiac Rhythm of Undetermined Mechanism

THE most successful results in the treatment of disorders of cardiac rhythm are possible only when the precise nature of the disorder of rhythm is established. Clinically, a paroxysm of auricular and ventricular tachycardia may appear similar. In both cases, the patient is seized with an attack of palpitation with a rapid heart action of about 200 a minute and regular rhythm. Digitalis is the most effective drug against auricular tachycardia. Quinidine is the only drug effective against ventricular tachycardia, and in this condition there is the possibility that digitalis may do harm. One cannot, therefore, emphasize too strongly the importance of an accurate differential diagnosis. A precise differential diagnosis, however, is not always possible. The physician may be without sufficient experience in the use of the carotid sinus pressure technic or in the reading of the electrocardiogram. An electrocardiograph may not be accessible. On clinical examination, frequent premature contractions often resemble *auricular fibrillation. Auricular flutter with varying A-V* block is often indistinguishable from auricular fibrillation in the routine leads of the electrocardiogram. Paroxysmal auricular tachycardia which does not respond to carotid

pressure may be impossible to distinguish from some cases of nodal tachycardia or auricular flutter, even by experts with all the necessary equipment at their command. Auricular tachycardia, flutter, and sometimes auricular fibrillation, when associated with bundle branch block, may be impossible to distinguish from ventricular tachycardia.

The group in which a differential diagnosis cannot be made for one reason or another is a fairly large one. What is to be done in these cases? There is the suggestion that in the interest of safety, no attempt should be made here to apply specific agents, that the wisest course is to allay panic or other distress by a barbiturate or morphine, and temporise until the ectopic rhythm terminates spontaneously. While such treatment is sometimes adequate, there are many cases in which symptoms are very severe and circulatory disaster threatens. Cases of disordered rhythm in which the differential diagnosis between the various mechanisms cannot be made do not need to go without specific therapy which offers a high probability of success. Quinidine should be tried in these cases. While it is not equally effective in all, it is highly effective in the 6 common forms of disorders of rhythm in which a precise diagnosis is sometimes difficult or impossible to establish, namely, premature contractions, auricular tachycardia, nodal tachycardia, auricular flutter, auricular fibrillation, and ventricular tachycardia. Quinidine is the only drug which offers so much in the absence of a specific diagnosis. Treatment may be started with 0.4 Gm. (6 gr.) every three hours, and adjustments in the dose may be made in accordance with the guides suggested in the section on Dosage.

18

Angina Pectoris

QUINIDINE has been used for the control of cardiac pain in patients with coronary disease and the angina of effort. Doses of the order of 0.3 Gm. (5 gr.) three times daily have been tried. In animal experiments, there is evidence of direct depressant action on blood vessels causing relaxation, and blocking of the vagus which is believed to be the constrictor innervation of the coronary vessels. There is also evidence of blocking of an action of epinephrine which may indirectly increase cardiac work. Its power to increase the capacity for exertion (exercise tolerance test) in the patient with angina of effort has been tested and favorable responses have been published. The clinical evidence for the value of quinidine to control cardiac pain in patients subject to angina of effort is not satisfactory. More work on this subject and better controlled clinical experiments are needed.

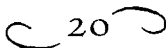
19

Coronary Thrombosis

QUINIDINE is used in patients with acute coronary thrombosis for the same purposes as in patients with other varieties of heart disease. The same doses and dosage plans are employed. There is no satisfactory proof that the tolerance of these patients to quinidine is different from that of others. The plans of dosage described in the section on Dosage allow for marked variations in tolerance among diseases and individuals.

There is one special aspect of the problem in patients with acute coronary thrombosis, and that relates to their marked tendency to develop ventricular tachycardia. Since such an attack is particularly hazardous in the acutely damaged heart, the prophylactic use of quinidine immediately after the diagnosis of acute coronary thrombosis, has been suggested. This is frequently done, and the drug is usually given in doses of 0.2 Gm. (3 grains) three times daily for this purpose. There is no doubt of the theoretical justification for such a practice, but there is no satisfactory clinical proof that it has value. Several factors need to be considered. The effective dosage for any particular case is not known in advance, and there is no way of establishing it until an attack occurs. In view of the variety of toxic effects of quinidine, it would not seem justifiable to use large doses prophylactically in a routine manner. I have, therefore, adopted a compromise plan of observing patients with acute coronary thrombosis with great care for the

earliest appearance of premature contractions, which often occur as a precursor of a paroxysm of ventricular tachycardia. *Quinidine is then started in a dose of 0.3 Gm. (5 gr.)* and repeated at intervals of six hours. If it proves effective in abolishing the premature beats, this dosage may be continued daily, otherwise the dosage is increased according to plans suggested in the section on Dosage. The most satisfactory strategy for meeting the hazard of ventricular tachycardia prophylactically by the use of quinidine is probably not yet established. There is need for systematic investigation of this problem. The pooling of data gathered according to preestablished criteria from many sources should prove useful, for in that way sufficiently large numbers of cases will become available for valid statistical study.



Thyrotoxic Cardiac Disorders

PATIENTS with hyperthyroidism are subject to the same disorders of rhythm as occur in other diseases. Hyperthyroid patients, however, are particularly prone to develop paroxysms of auricular fibrillation. These attacks usually subside when the Graves' disease is brought under control by one or another method, such as

iodine or propylthiouracil therapy, or subtotal thyrodectomy. In the meantime, the paroxysms may be a source of difficulty, causing panic, severe palpitation, and circulatory insufficiency. The attacks are particularly troublesome when they occur just before or shortly after the thyroid operation. These seizures are apt to be associated with a very rapid ventricular rate, which is likely to be unusually resistant to the slowing action of digitalis. Quinidine is useful to restore and maintain a normal rhythm in these critical states. There is some experience suggesting that the usual doses are not as effective in abolishing auricular fibrillation caused by Graves' disease, nor as effective in preventing recurrences. There is some suspicion of undue toxicity of quinidine in a severe hyperthyroid state. This experience has, however, not been uniform, and observations have been made which indicate that these patients have a higher tolerance for quinidine than normal persons. There are some who do not advocate the use of quinidine to control the paroxysms of auricular fibrillation in the thyrotoxic patient, chiefly on the grounds that the drug is not very effective here, and the condition is temporary and usually subsides when the hyperthyroidism is brought under control. It is my belief, however, that the failures are often a matter of dosage, and it is our practice to use quinidine in paroxysmal auricular fibrillation which occurs as part of the hyperthyroid state, for the purpose of abolishing the attack and preventing recurrences. The dosage plans are similar to those described in the section on Dosage.

The paroxysmal variety of auricular fibrillation is here also to be distinguished from the chronic state of auricular fibrillation. If the abnormal rhythm has persisted a long time, it should be allowed to continue and digitalis is employed in the endeavor to slow the ventricular rate. The

earliest appearance of premature contractions, which often occur as a precursor of a paroxysm of ventricular tachycardia. Quinidine is then started in a dose of 0.3 Gm. (5 gr.) and repeated at intervals of six hours. If it proves effective in abolishing the premature beats, this dosage may be continued daily, otherwise the dosage is increased according to plans suggested in the section on Dosage. The most satisfactory strategy for meeting the hazard of ventricular tachycardia prophylactically by the use of quinidine is probably not yet established. There is need for systematic investigation of this problem. The pooling of data gathered according to preestablished criteria from many sources should prove useful, for in that way sufficiently large numbers of cases will become available for valid statistical study.

20

Thyrotoxic Cardiac Disorders

PATIENTS with hyperthyroidism are subject to the same disorders of rhythm as occur in other diseases. Hyperthyroid patients, however, are particularly prone to develop paroxysms of auricular fibrillation. These attacks usually subside when the Graves' disease is brought under control by one or another method, such as

nodal, or ventricular tachycardia; auricular flutter or fibrillation; ventricular fibrillation; heart block; cardiac arrest. Their appearance is unpredictable. No stage of the anesthesia or operation is immune. The induction stage of anesthesia is an especially vulnerable period, but the disorders frequently occur only after deep and prolonged anesthesia with extensive surgical manipulation, or during the stage of recovery.

All the volatile anesthetic agents in common use produce them, such as ether, nitrous oxide, ethylene, ethyl chloride, chloroform, and cyclopropane. Cyclopropane behaves much like chloroform, sensitizing the heart in such a manner that minute doses of epinephrine give rise to ventricular tachycardia and fibrillation.

Surgical procedures, through reflexes or other factors not well understood, may also bring about disorders of rhythm. Certain kinds of operations are more effective than others in this respect. Abnormal rhythms are especially frequent in surgery of the heart and lungs. They present a conspicuous problem in thyroid operations in which the chief cause may be manipulation of the nerves in the region of the carotid sinus or sheath. Their frequent occurrence in operations on the biliary tract and upper portions of the gastro-intestinal tract are in line with experimental and clinical observations indicating that these regions are rich sources of reflexes which disturb the rhythm of the heart.

Responsibility for the disorder of rhythm cannot always be accurately placed, since both surgical manipulation and the anesthetic agent are involved simultaneously. It is probable that in many cases several factors contribute, such as pre-anesthetic anxiety and panic, sudden rise of the blood pressure, pre-anesthetic medication, the toxicity of the anesthetic agent, reflexes from the operative field, in-

hazards of restoring a normal rhythm in long-standing auricular fibrillation of hyperthyroidism are, in all probability, similar to those in other states. These have been described in the section on Auricular Fibrillation.

At this point, attention may be called to the fact that the normal rapid heart action (sinus tachycardia) of hyperthyroidism is not an indication for quinidine. There is the fact that large doses, as high as 3 to 4 Gm. daily, or even larger, may lower the basal metabolism and slow the heart rate. Such a remission is not nearly as satisfactory as that obtained by iodine or propylthiouracil. It is not recommended as a routine practice.

21

Anesthesia and Surgery

GENERAL anesthesia and surgical operations often disturb the mechanism of the heart beat. If electrocardiograms are taken at frequent intervals, disorders of the beat may be detected in about 75 per cent of the patients. There is indication that patients with hypertension or heart disease are somewhat more susceptible. All the well-known types of changes are encountered: sinus bradycardia or tachycardia; exaggerated sinus arrhythmia; displacement of the pacemaker from the sinus node to the auricle, A-V node, or ventricle; premature contractions of various origins; coupled rhythm; auricular,

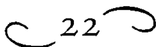
of factors only occasional ventricular premature contractions are produced; with another, they may increase to form a coupled rhythm; and with still another, premature contractions may advance to ventricular tachycardia, the precursor of fatal ventricular fibrillation. The instability of the factors in surgery and anesthesia is revealed by the fleeting character of the ectopic rhythms, and the frequency of several types of abnormal rhythm in the same individual during different periods of the same operation. A few harmless premature contractions would constitute no reason for concern, if it were not for the possibility that, under these conditions, they might be followed by a more threatening disorder of rhythm before the patient is through either with the operation or the anesthesia.

The effects of the various factors in surgery and anesthesia which give rise to abnormal rhythms are usually reversible. This is important from the standpoint of treatment. Temporary interruption of surgical manipulation, an increase in oxygen supply, or a shift to another anesthetic agent may abolish premature contractions, or shorten a paroxysm of a major ectopic rhythm, such as ventricular tachycardia. These are the primary measures in treatment. When their application is not feasible, or when they prove unsuccessful, one may turn to specific drugs. In this connection, it is well to mention that such drugs are not altogether safe, that in the majority of cases the ectopic rhythm is fleeting and terminates spontaneously, that the use of the electrocardiogram for an accurate differential diagnosis of the ectopic rhythm during surgical operations presents technical difficulties, and that the conversion of an irregular rhythm into a regular one by a particular drug is not necessarily advantageous, for the irregular rhythm may have been due to the relatively inconsequential premature contractions, while the regular one may represent the

creased carbon dioxide, anoxemia, trauma, hemorrhage, and shock.

Disorders of the mechanism of the heart beat in surgery and anesthesia have, in some respects, the same significance as similar disorders occurring under other conditions. It was pointed out in previous chapters that, in persons with a structurally normal heart, or even in persons with heart disease, the sudden onset of a rapid heart rate, as in a paroxysm of auricular tachycardia or fibrillation, is usually of no serious consequence, but that in some patients with hypertension, coronary sclerosis, or other forms of heart disease, especially in an advanced stage, it may impair the coronary circulation or cardiac function sufficiently to bring on cardiac or peripheral circulatory failure. Regardless of the conditions under which they occur, the need, in such cases, for prompt and vigorous measures to terminate the ectopic rhythm is self-evident. Attention was also called to the fact that premature contractions constitute a minor disorder, the most common among the abnormal rhythms. They are harmless and, if the patient is without a disturbing awareness of them, they may be allowed to go without treatment. The major forms of disordered mechanism, such as auricular fibrillation, ventricular tachycardia, and ventricular fibrillation, comprise but a small proportion of the abnormal rhythms during surgery and anesthesia, probably less than 5 per cent. Premature contractions here also constitute the vast majority, and they are equally harmless from the standpoint of the mechanics of the heart and circulation. However, the factors they often represent are potentially more dangerous. They signify that the heart is exposed to such influences as trauma, reflexes, dehydration, anoxemia, or a toxic anesthetic agent, unstable combinations of elements capable of causing minor or serious cardiac disorders. With one factor or combination

quinidine sulfate in propylene glycol by intramuscular injection in man. Preliminary observations disclosed a curve of action for quinidine, when given in this way, which would seem especially suited for use in prophylaxis. Experience is needed to establish the most favorable plan of dosage, which would take into account individual differences in susceptibility. From our present knowledge, I would suggest an intramuscular dose of 0.3 Gm. (5 gr.) to 0.4 Gm. (6 gr.) every 4 hours for 3 or 4 doses, with the last dose about 1 hour, prior to the anesthesia, as a means of providing a fairly effective concentration in the heart at the time it is most needed. This dose may then be continued at intervals of 4 to 6 hours until the danger of a disorder of rhythm has passed.



Combined Use of Quinidine and Digitalis

WITH the introduction of quinidine for the treatment of auricular fibrillation, there soon arose the question of the relation between the actions of this drug and digitalis, since up to that time digitalis alone was widely used in the treatment of auricular fibrillation. The difference in purpose of the two drugs was well appreciated. Digitalis was used for the control of heart failure and for the slowing of the heart rate in patients

more hazardous rhythm of ventricular tachycardia induced by the drug. In view of the foregoing and of the fact that ectopic rhythms which appear during surgery and anesthesia are rarely fatal, the routine use of drugs in the endeavor to terminate an abnormal rhythm as soon as it appears cannot be satisfactorily defended.

Several drugs have been tried with varying degrees of success. Quinidine is highly effective in the majority of disorders of rhythm which occur during surgery and anesthesia. In a previous section, attention was called to its use even in the absence of a differential diagnosis. In extremely urgent situations, it may be given intravenously. The method of injection which provides the highest chance of success with a minimum of risk is described in the section on Ventricular Tachycardia.

In less urgent situations, the intramuscular route will suffice. The preparation of choice for this purpose is quinidine sulfate in propylene glycol (see section on Preparations). A dose of 0.4 Gm. (6 gr.) produces its maximum effect in about an hour. The dose may be repeated in accordance with the principles described in the section on Dosage, until the desired result is obtained.

Prophylaxis is an important aspect of therapy of disorders of rhythm in surgery and anesthesia. For this purpose quinidine holds out the greatest promise. Little is known of this phase of the problem: the most favorable cases, route of administration, or dosage. The routine use of quinidine prophylactically in cyclopropane anesthesia has been suggested. The regimen of an oral dose of 0.3 Gm. (5 gr.) at night, repeated in the morning before operation, and additional doses as necessary, has been used as a routine in cardiac surgery. The oral route would not seem to be the most favorable one in surgery and anesthesia. There is always the risk of vomiting or diarrhea. Modell, Gluck, and I carried out some experiments with

which leave little ground for a secure decision as to the wisdom of either using them together or avoiding their combined use. With respect to the action on refractory time, quinidine prolongs it, while digitalis, through both vagal stimulation and direct action on auricular muscle, usually shortens it, but by the action of increased force of muscular contraction, digitalis may also prolong refractory time. On the speed of conduction in the auricle, quinidine acts to slow conduction, while digitalis tends to accelerate it. The action on conduction, in the case of digitalis, would operate in the direction of terminating a circus movement, since more rapid conduction may create smaller circus pathways, while, in the case of quinidine, the action on conduction would operate to perpetuate a circus movement. The action of quinidine to prolong the refractory period and of digitalis to speed up conduction, operating simultaneously, would make the combination of the two drugs more effective in terminating fibrillation of the auricles than quinidine alone. There would remain the question how often such selective combination of actions can be secured.

There are other questions which leave the matter of the combined use of the two drugs in auricular fibrillation in a state of uncertainty. There is the point that the antifibrillary effect of drugs may be due to an as yet undetermined mechanism, not necessarily related to measurements of refractory time or conduction speed. There is the fact that while quinidine often terminates fibrillation of the auricles, very large doses sometimes give rise to fibrillation of the ventricles. It is well known that digitalis sometimes precipitates auricular fibrillation in patients with a normal rhythm, and there is some indication that digitalis occasionally terminates fibrillation in the auricles, possibly the consequence of such factors as improved myocardial func-

with auricular fibrillation, while quinidine was used in the endeavor to abolish the fibrillation in the auricles and establish a normal rhythm. Are the actions of these two drugs on the heart so independent of each other that their use at the same time would produce results similar to those of each alone? Do they exert any antagonistic actions so that the presence of one might erase the effects of the other? Or are the actions of the two drugs such, that when they operate simultaneously, the effects might summate or potentiate, or give rise to new effects, therapeutic or toxic, which might not be predictable from the known actions of each? These were the kind of questions that have arisen, and a sizable literature bearing on them now exists.

It can be stated at once that some of the answers are inconclusive from both experimental and clinical experience. Practical recommendations are not in accord. First, there are those who advise against the use of the two drugs simultaneously, and advocate that failure should be brought under control by means of digitalis alone, and that quinidine should be used after an interval, to abolish the abnormal rhythm. This is based on certain established antagonistic actions of the two drugs. Second, there are those who advocate the combined use of the two drugs on the grounds that their antagonistic action with respect to fibrillation of the auricles can be overcome by a slight increase in the dose of quinidine. Finally, there are those who have failed to observe any practical antagonism between the two drugs. They have secured the action of quinidine in abolishing auricular fibrillation with similar doses in patients who had been digitalized as in those who had not.

An examination of the experimental observations relating to both drugs reveals a complexity of actions for each, and a greater complexity when the two are used together,

not predictable. In animal experiments in which the cardiac rhythm remained normal after large doses of digitalis, small doses of quinidine sometimes and quite unexpectedly produced ventricular tachycardia, and in others, a moderate dose of quinidine, after a toxic dose of digitalis, unexpectedly produced complete cardiac arrest. These results followed doses of quinidine which caused no such effects on the heart that was free of digitalis. The most striking result was seen in the experiment in a dog, in which a total of 40 mg. of quinidine per Kg. intravenously caused only marked sinus acceleration, but in one poisoned by digitalis, as little as 3 mg. per Kg. caused prompt sinus arrest.

The use of the two drugs together in human cases has produced undesirable results, sometimes predictable, but at other times not easily explained. It is well known that in patients with auricular fibrillation in whom moderate doses of digitalis have slowed the apex rate to about 80 a minute, an oral dose of 0.8 Gm. of quinidine may erase most of the digitalis slowing and accelerate the rate to 120 a minute or more. The reverse result is occasionally encountered. A striking example may be cited. A male patient, age 64, with arteriosclerotic and hypertensive heart disease was subject to paroxysms of auricular fibrillation during which the electrocardiogram showed a bundle branch block. In these attacks, the ventricular rate was 180 a minute. The patient had mild symptoms of congestive failure, and during the attacks of fibrillation, the failure was greatly intensified. At first it was decided to use digitalis to encourage the fibrillation to continue and to maintain a slow ventricular rate at about 70 a minute. This proved only partially successful, for with full doses of digitalis the heart rate slowed to 70 a minute, but the mechanism continued to shift back and forth between

tion or marked shortening of the pathways in the complex circus movement, which renders the fibrillation unstable. Out of these actions of the two drugs, combinations of effects are possible which might either promote or abolish fibrillation. In the A-V node, digitalis slows the speed of conduction by reflex vagal stimulation and by direct action on the node, while quinidine exerts two conflicting actions: one, to slow conduction by direct depression of the node; and two, to accelerate conduction by blocking vagal function. When digitalis is first used to slow the ventricular rate in patients with auricular fibrillation, and quinidine is then given to abolish the fibrillation of the auricles, there may result either further slowing of the heart rate due to the actions of the two drugs in blocking A-V conduction, or acceleration of the heart rate may occur due to the vagal depression by quinidine erasing the vagal stimulation by digitalis. On the contraction of heart muscle, digitalis acts in small doses to increase the force and in excessive doses to diminish the force, while quinidine exerts no appreciable action on force in small doses, but also acts to diminish force in large doses. These and other theoretical possibilities exist and have been observed in experiments.

In animals which received large doses of digitalis sufficient to produce ventricular tachycardia, quinidine abolished the ventricular ectopic rhythm. The result in some was a sinus rhythm which was rapid because of the vagal blocking action of quinidine. When the dose of digitalis caused complete A-V block as well as ventricular tachycardia, the quinidine abolished the latter, and the result was ventricular standstill because the block prevented the passage of impulses from the auricle to the ventricle. Such results were predictable, but the combined use of the two drugs in animals has produced results which were

oped premature ventricular contractions and congestive failure with mild attacks of nocturnal dyspnea in two and three weeks, respectively, after the coronary thrombosis. Both were digitalized and the symptoms of failure diminished, but when the premature contractions continued and recurred in groups of 2 or 3 beats, it was decided to attempt to control them by means of quinidine. One patient received 0.2 Gm. (3 gr.) every four hours, and the other, 0.3 Gm. (5 gr.) three times a day. After the fourth day, one of them described an attack of syncope while in bed. The attack was over by the time he was seen by the nurse, but the effect of loss of sphincter control presented sufficient confirmatory evidence. On the second day, the other developed an attack while the nurse was in the room. His gaze became fixed, respiration stopped, the pulse disappeared, and a convulsion ensued. In both cases, the cardiac arrest recurred during a subsequent trial of both drugs. Further observation in both patients established the fact that the reaction could not be produced by the previous therapeutic doses of digitalis or quinidine alone.

In the reports on the use of quinidine to abolish auricular fibrillation, numerous cases of ventricular tachycardia have been encountered. It is noteworthy that most of these occurred in patients who had previously been digitalized.

The administration of quinidine and digitalis simultaneously is widely practiced, especially in the attempt to abolish auricular fibrillation. It has proved a successful routine in the hands of many observers, and this alone indicates that the dominant actions of the two drugs are neither sufficiently antagonistic to interfere with the therapeutic results in the majority of cases, nor are they such as to lead to frequent serious accidents. I have had an occasional stubborn case in which the prevention of paroxysms of auricular fibrillation seemed impossible by quini-

auricular fibrillation and normal sinus rhythm, both at a rate of about 70 a minute. Since the amount of digitalis necessary to achieve this result was sufficient to impair the appetite, the maintenance dose was slightly reduced, but this resulted in another difficulty, namely that when the fibrillation recurred, the heart rate was again very rapid. It was, therefore, decided to keep the patient moderately digitalized and attempt to stabilize the normal sinus rhythm by means of quinidine. The quinidine was begun when the rhythm was auricular fibrillation and apex rate 86 a minute. A dose of 0.3 Gm. (5 gr.) of quinidine three times daily acted in a manner synergistic with the digitalis and slowed the apex rate to 52 a minute. On the third day, the normal sinus rhythm was restored, but the rate of the sinus node was also markedly reduced, as low as 46 a minute. In this patient, therefore, both the S-A node and the A-V node were unusually susceptible to the depressant action of quinidine, and it was found impossible to use enough digitalis to control the failure together with enough quinidine to maintain a normal rhythm, without excessive slowing of either the sinus rate or the ventricular rate in auricular fibrillation. When we attempted to continue the two drugs, the patient developed long sinus pauses during one of which coma followed by a convulsion occurred. The tendency to extreme bradycardia disappeared promptly when the quinidine was discontinued. This is a fairly clear case of synergistic depression by the combined use of digitalis and quinidine on the S-A and A-V nodes. Cases of cardiac arrest following quinidine have been reported. I encountered two such instances in patients receiving both digitalis and quinidine, in whom the evidence was fairly conclusive that the cardiac arrest was due to the combined action of the two drugs. They were both patients with coronary artery disease, who devel-

drug. Several of the extracardiac toxic symptoms, those grouped under the term "cinchonism," such as impairment of hearing, ringing in the ears, or clouding of vision, may not be detected in infants or young children. In these, more dependence is placed on electrocardiographic changes to detect early toxicity, namely, the appearance of 40 or 50 per cent prolongation in the QRS time, or premature beats of multiple foci.

There is no satisfactory evidence on the question of the tolerance of infants or children to quinidine. From the practical standpoint, this is not very important, because a course of treatment calls for establishing the necessary dosage in each case by the repetition of a safe dose at such intervals as will lead to gradual cumulation of the drug until an effective level is reached. In the light of the limited knowledge existing at the present time, it is expedient to use approximately the adult dose on a body weight basis in infants and children. Accordingly, in the endeavor to abolish an abnormal rhythm, the most satisfactory routine at the start is 3 mg. per pound of body weight given orally every three hours, and continued until either the abnormal rhythm is terminated, or vomiting, diarrhea, or prolonged QRS time appears. In the event of factors precluding the oral route, quinidine in propylene glycol may be given intramuscularly in similar dosage (see section on Preparations).

There is some limitation in the matter of dosage form. Adults usually receive the drug in the form of tablets or capsules. It is feasible in some cases to crush the tablet or place the powder in a teaspoon and administer it suspended in milk. A suspension of quinidine is sometimes more practicable. For this purpose, a 5 per cent suspension of quinidine sulfate in chocolate syrup (of the soda fountain) may be prepared. This thick syrup masks the bitter taste fairly well.

dine until the patient was digitalized. The fact remains, however, that their combination in certain doses and in particular individuals appears to have been responsible for some hazardous effects, and the experimental evidence is fairly strong that quinidine in otherwise nontoxic doses may sometimes produce unexpected and disastrous results in the heart poisoned by digitalis. These are the reasons for the position I have adopted in this matter—to avoid the simultaneous use of quinidine and digitalis wherever possible, especially where large doses of both may be necessary.

23

Quinidine in Children

THE indications for quinidine in infants and children are the same as those in adults. It is used in the treatment of premature contractions, auricular tachycardia, auricular flutter, auricular fibrillation, and ventricular tachycardia. There are, however, special problems applicable to infants and children. These relate to dosage, preparations, and guides to toxicity.

The plan of quinidine dosage which has been described involves the repetition of a safe dose at fixed intervals with a view to accumulating enough of the drug in the heart to bring the abnormal rhythm under control. The single dose is repeated until the therapeutic objective is reached, or *minor* toxic effects result which call for interruption of the

work of Lewis and his collaborators gave quantitative expression to some of these differences and the conclusion was drawn that, gram for gram, quinidine is 5 to 10 times as potent as quinine. They compared various compounds with respect to their action in slowing the circus movement in patients with auricular fibrillation. They measured the slowing caused by a large dose of quinidine and a similar dose of quinine, and considered the ratio of the two effects as representing the ratio of potency of the two drugs. For example, when 0.6 Gm. of quinidine slowed the auricle 250 a minute and a similar dose of quinine slowed it only 50 a minute, they concluded that the first was 5 times as potent as the second. It is now known that this is not a valid method of bioassay. The relationship between the doses and the responses for each drug in a bioassay, when charted, makes a curve which has a steep slope in the middle and flattened portions at each end. Drugs are compared in the dosage range shown by the steep, or sensitive, portion of the curve. There, a 10 per cent increase in dose may produce 100 per cent increase in effect. If the doses are too small or too large and fall in the range of the flattened portions of the curve, the insensitive areas, 100 per cent increase in the dose may produce little or no increase in effect, and as a result, differences in potency of the two compounds may escape detection. Lewis and his collaborators used ceiling doses of quinidine in their comparisons. The second defect lies in their seeking out the dissimilar magnitude of effects produced by similar doses of drug rather than the differences in doses necessary to produce similar effects. In the dosage-response curve, the ratio of effects differs with the size of the dose. If, for example, 0.2 and 0.4 Gm. of quinidine fall in the sensitive steep portion of the curve, the 0.4-Gm. dose may produce twice as much slowing of the circus movement as the 0.2-

24

Quinidine and Related Compounds

QUINIDINE of commerce is the natural quinidine obtained from the cinchona bark. It is a mixture of quinidine with approximately 15 per cent of dihydroquinidine. The relative potency of different cinchona alkaloids on the heart in man presented an urgent problem during World War II, when the East Indies fell into the hands of the Japanese, who shut off the supply of these drugs from the rest of the world. The shortage could be overcome by the conversion of quinine into quinidine and dihydroquinidine, but this raised the question as to whether synthetic quinidine was equally as effective as the natural quinidine, and the further question as to the relative effectiveness of synthetic quinidine and dihydroquinidine in disorders of cardiac rhythm. There are some animal experiments indicating that dihydroquinidine is several times as potent as quinidine on the heart.

The early observations in humans suggested that the various alkaloids of the cinchona group are not equally effective on the heart, and that quinidine is more potent than quinine. Some of the results were inconclusive Those obtained by Wenckebach and by Frey were based on general experience that quinidine was more frequently successful than quinine in controlling ectopic rhythms. The

that idiosyncrasy to quinine and other levorotatory compounds, in the form of urticaria, coryza, or asthmatic attacks, may sometimes be avoided by the use of the dextroisomers, quinidine and cinchonine.

25

Preparations of Quinidine

THE preparation of quinidine which is most widely used by the oral route is quinidine sulfate in the form of capsules or tablets. Quinidine sulfate U.S.P. is a white crystalline powder with a very bitter taste. It has a solubility of approximately 1:100 in water and 1:10 in alcohol. Its solution darkens on exposure to light. For those who cannot take capsules or tablets, a 5 per cent suspension in chocolate syrup (of the soda fountain) may be prescribed. The thick syrup masks the bitter taste fairly satisfactorily. The usual dose of 0.4 Gm. (6 gr.) would be represented by 2 teaspoonfuls of the suspension. This preparation is especially useful for infants and children.

For intravenous injection, a unit of one ampule containing 0.2 Gm. (3 gr.) of quinidine sulfate powder and another ampule containing 20 cc. of sterile distilled water to be made up into a 1 per cent solution just before use, is practicable. This dilute solution and a 24- or 26-gauge

Gm. dose; whereas, in the case of 0.8 and 1.6 Gm., falling in the ceiling portion of the curve, the effects of the two *doses may be indistinguishable. Their method, therefore,* as applied to the relative potency of two compounds, would yield a series of ratios, none of which might reflect the true relative potency of two drugs.

These defects were avoided in a recent study in our clinics in which several cinchona alkaloids were compared with respect to their effect on the speed of the circus movement in patients with auricular fibrillation. The results showed that the potency of natural quinidine is the same as synthetic quinidine and dihydroquinidine, that these compounds are twice as potent as quinine and cinchonidine on the heart, and that cinchonine is the weakest of all.

Two other points of interest issued from these studies. One was the indication of a qualitative difference in the mechanism of action of quinidine and quinine as shown by a difference in the level of the ceiling effect. The ceiling for quinidine was found to be about twice as high as that for quinine. Within a range of action represented by about 20 per cent slowing of the auricle, the same result may be obtained by either drug, if twice as much quinine as quinidine is given. If more intense action such as is represented by 40 per cent slowing of the auricle is necessary to produce the therapeutic result, only quinidine can be used, since such a degree of action cannot be obtained with quinine, regardless of the dose.

The other point relates to the toxic actions, gastrointestinal irritation and symptoms of cinchonism. These actions in the two drugs do not run strictly parallel. A particular effect on the heart which is attended by unpleasant side-effects with one of the drugs, is in some patients obtained with the other without unpleasant effects.

The work of Dawson and his collaborators has shown

26

Routes of Administration

QUINIDINE in the treatment of disorders of cardiac rhythm is administered by the oral route in the vast majority of cases. As in the case of other cinchona alkaloids, most of its preparations are too irritant for subcutaneous use or for routine intramuscular injection. There is indication that absorption after an intramuscular injection is only slightly faster than after oral administration. The rectal route is not satisfactory. The local irritation in the rectum may lead to an inflammatory reaction, and even solutions of 0.5 to 1 per cent may not be retained long enough for effective absorption.

The intravenous route may be used in cases in which there is great urgency, or in those in which the oral route is not feasible. For this purpose, a freshly prepared 1 per cent solution of quinidine sulfate in physiologic saline may be employed. This solution is neutral or slightly alkaline. It darkens on exposure to light, although there is doubt whether this change in color involves any material change in potency. Satisfactory solutions of quinidine sulfate are not available in commerce. It would be well to have at hand a unit consisting of an ampule of 0.2 Gm. of the quinidine sulfate powder and an ampule containing 20 cc. of sterile distilled water for the preparation of a 1 per cent solution of quinidine sulfate prior to injection. There are risks in the use of quinidine by intravenous injection because of the toxicity of this drug in high concentration

hypodermic needle help to insure slow intravenous injection.

A 12 per cent solution of quinidine hydrochloride with antipyrine and urea has been used by intramuscular injection with some success, but this solution is not stable and crystallization tends to form in the ampule after prolonged storage.

A 6.5 per cent (0.65 Gm. in 10 cc.) solution of quinidine lactate for intravenous and intramuscular injection has been prepared. The lactate is more soluble than the sulfate. Some solutions of this compound turn yellow. The intramuscular injection is painful. More experience in its use is needed.

A 20 per cent solution of quinidine sulfate in propylene glycol (0.2 Gm. in 1 cc.) has been prepared for intravenous and intramuscular injection. This solution remains colorless and its intramuscular injection is substantially painless. We have tried this material in several patients by the intramuscular route. It produced either no pain or negligible tenderness in the area of injection. This preparation offers great promise for meeting the problems of parenteral administration of quinidine. There is need for more experience in its use.

Bibliography

1906

1. GUSTETTER, A. L. Quinin in pneumonia. *J.A.M.A.* 46: 799, 1906.

1918

2. FREY, W. Ueber Vorhofflimmern beim Menschen und seine Beseitigung durch Chinidin. *Berl. klin. Wchnschr.* 55:450, 1918.

1920

3. SCHOTT, E. Zur Frage der Chinidintherapie. *Deutsch. Arch. f. klin. Med.* 134:208, 1920.

1921

4. COHN, A. E., and LEVY, R. L. Experimental studies on the pharmacology of quinidin. *Proc. Soc. Exper. Biol. & Med.* 18:283, 1921.
5. DRURY, A. N., and ILIESCU, C. C. The restoration of the normal cardiac mechanism in cases of auricular fibrillation by means of quinidine sulphate. *Brit M. J.* 2 511, 1921.
6. FREY, W. Chinidin zur Bekämpfung der absoluten Herzunregelmässigkeit (Vorhofflimmern). *Deutsch. Arch f klin. Med.* 136 70, 1921.
7. FREY, W., and HAGEMANN, E. Klinische und experimentelle Daten über toxische Chinidinwirkung. *Ztschr. f. d. ges. exper. Med.* 25:290, 1921.
8. GROEDEL, F. M. Ungünstige Chinidinwirkung bei Vollkommenen Herzblock. *Therap. d. Gegenw.* 62:172, 1921.
9. LEWIS, T, DRURY, A. N., and BULGER, H. A. Observations upon flutter and fibrillation. VI. The refractory period and rate of propagation in the auricle: their relation to block in the auricular walls and to flutter, etc. *Heart* 8 83, 1921.
10. LEWIS, T., DRURY, A. N., ILIESCU, C. C., and WEDD, A. M. The manner in which quinidine sulphate acts in auricular fibrillation. *Brit. M. J.* 2:514, 1921.

in the blood stream. This route of administration should be used only by those who have had experience with it. The injection is made very slowly, and the observer listens to the heart for signs of effect during the course of the injection. The details are described in the section on the treatment of ventricular tachycardia, in which condition intravenous quinidine is more often needed than in any other disorder of cardiac rhythm.

There is available in commerce an ampule of quinine dihydrochloride. This is the most soluble of all the salts of the cinchona alkaloids, 1 part in 0.6 part of water. This has been used intramuscularly in a 10 per cent solution in doses of 0.5 Gm. in 5 cc. It is effective but gives rise to painful indurated areas in the muscle. It is also sometimes used by intravenous injection in a 0.5 per cent solution, the dilute solution helping to insure very slow injection. One must bear in mind the fact that quinine, having a lower ceiling of action than quinidine, may in some cases prove ineffectual as a substitute for quinidine.

Other preparations for intramuscular injection are mentioned in the previous section. The ampule containing quinidine dissolved in propylene glycol, mentioned there, deserves special attention.

23. Reid, W. D. Respiratory paralysis following quinidin therapy. *J.A.M.A.* 79 1974, 1922.

1923

24. Burwell, C. S., and Dieuaide, F. R. Clinical experience with quinidin. *Arch Int. Med.* 31:518, 1923.
25. Clark-Kennedy, A. E. Quinidine in the treatment of auricular fibrillation. *Quart J. Med.* 16:204, 1923.
26. Fraser, F. R. Discussion on the action of quinidine in cases of cardiac disease *Proc. Roy. Soc. Med.* 16 part 3· p. 25, 1923.
27. Korns, H. M. An experimental and clinical study of quinidin sulphate: I. Experimental. *Arch. Int. Med.* 31 15, 1923.
28. Viko, L. E., Marvin, H. M., and White, P. D. A clinical report on the use of quinidin sulphate *Arch Int. Med.* 31:345, 1923.
29. Wenckebach, K. F. Cinchona derivatives in the treatment of heart disorders *J.A.M.A.* 81.472, 1923
30. Wolferth, C. C. The control of paroxysmal tachycardia by quinidine sulphate. *New York State M. J.* 117 552, 1923
31. Wolferth, C. C. Depression of cardiac conductivity during quinidin therapy. *J.A.M A.* 80 1289, 1923

1924

32. Carr, J. G., and Spoeneman, W. H. Untoward effects of quinidin. *Illinois M. J.* 46 445, 1924.

1925

33. Gilbert, M Case of paroxysmal tachycardia cured by quinidin sulphate. *Schweiz. med. Wchnschr.* 55.1207, 1925.
34. Gordon, B., Matton, M., and Levine, S. A. The mechanism of death from quinidine and a method of resuscitation· an experimental study. *J. Clin. Investigation* 1 497, 1925.
35. Junkmann, K. Uber die pharmakologische Beeinflussung der Dynamik des Froschherzens. *Arch. f. exper. Path. u. Pharmakol.* 105:169, 1925.

11. Lewis, T., Drury, A. N., Iliescu, C. C., and Wedd, A. M. Observations relating to the action of quinidine upon the dog's heart; with special reference to its action on clinical fibrillation of the auricles. *Heart* 9:55, 1921.

1922

12. Cohn, A. E., and Levy, R. L. Experiments with quinidine on conduction and on the refractory period in the dog's heart. *Proc. Soc. Exper. Biol. & Med.* 19:174, 1922.
13. Drury, A. N., Horsfall, W. N., and Munly, W. C. Observations relating to the action of quinidine upon the dog's heart; the refractory period of, and conduction in, ventricular muscle. *Heart* 9 365, 1922.
14. Grant, R T., and Iliescu, C. C. Comparison of the action of quinidine with other cinchona alkaloids in auricular fibrillation. *Heart* 9 289, 1922.
15. Hamburger, W. W., and Priest, W. S., Jr. The quinidin treatment of auricular fibrillation. *J A.M.A.* 79 187, 1922.
16. Kerr, W. J., and Bender, W. L. Paroxysmal ventricular fibrillation with cardiac recovery in a case of auricular fibrillation and complete heart block while under quinidine sulphate therapy *Heart* 9 269, 1922
17. Levy, R. L. Clinical studies of quinidin. IV. The clinical toxicity of quinidin. *J.A.M.A.* 79:1108, 1922.
18. Levy, R. L. Clinical studies of quinidin. II. Alterations in the cardiac mechanism after administration of quinidin to patients with auricular fibrillation with consideration of certain toxic effects of the drug. *Arch. Int. Med.* 30:451, 1922.
19. Levy, R. L. Clinical studies of quinidine. *New York State M. J.* 22.276, 1922
20. Lewis, T. The value of quinidine in cases of auricular fibrillation and methods of studying the clinical reaction. *Am. J. M. Sc.* 163.781, 1922.
21. Lewis, T. The actions of atropine and quinidine in fibrillation of the auricles clinical and experimental studies. *Am. J. M. Sc.* 164:1, 1922.
22. Lewis, T., Drury, A N., Wedd, A. M , and Iliescu, C. C. Observations upon the action of certain drugs upon fibrillation of the auricles. *Heart* 9:207, 1922.

49. MAYNARD, E. P. Five years' experience in the treatment of chronic auricular fibrillation with quinidin sulphate. *Am. J. M. Sc.* 175:55, 1928.

50. NELSON, E E. Studies on quinine and quinidine. V. Do they have a specific action on autonomic nerve ends? *Proc. Soc. Exper Biol. & Med.* 25:499, 1928.

51. PARKINSON, J., and CAMPBELL, M. The quinidine treatment of auricular fibrillation. *Quart J. Med.* 22 281, 1928.

1929

52. DOCK, W. Transitory ventricular fibrillation as a cause of syncope and its prevention by quinidine sulphate. *Am. Heart J.* 4 709, 1929.

53 LEVINE, S A., and FULTON, M. N. The effect of quinidine sulphate on ventricular tachycardia. *J.A M A.* 92:1162, 1929.

54. WOLFF, L, and WHITE, P. D. Auricular fibrillation. Results of seven years' experience with quinidine sulphate therapy. *Arch. Int. Med.* 43 653, 1929.

1930

55. DAWSON, W. T., and GARBADE, F. A. Idiosyncrasy to quinine, cinchonidine and ethylhydrocupreine *J.A.M.A.* 94:704, 1930.

56. DAWSON, W. T, and GARBADE, F. A. Idiosyncrasy to quinine, cinchonidine, and ethylhydrocupreine and other levorotatory alkaloids of the cinchona series further chemical delimitation of the idiosyncrasy, alteration in sensitiveness. *J. Pharmacol. and Exper Therap.* 39 417, 1930.

57. PARKINSON, J., and CAMPBELL, M. Paroxysmal auricular fibrillation. *Quart. J. Med.* 24 67, 1930

58. SPIRO, H., and NEWMAN, W. W Quinidin—some toxic effects. *Calif. and Western Med.* 32:398, 1930.

1931

59. DAWSON, W. T., and NEWMAN, S P Acquired allergic coryzal reaction to quinine but not to quinidine or quitenine. *J.A.M.A.* 97.930, 1931.

60. WHITE, P. D., and CAMP, P. D. The status anginosus induced by paroxysmal auricular fibrillation and paroxysmal tachycardia. *Am. Heart J.* 7.581, 1931.

36. SMITH, F. J., and CLARKE, N. E. Quinidin in the treatment of auricular fibrillation, established, paroxysmal and transient. *Arch. Int. Med.* 36:838, 1925.

37. WHITE, P. D, and SPRAGUE, H. B. Cases illustrating the indications for the use of quinidine sulphate in heart disorders. *Boston Med. and Surg. J.* 193:91, 1925.

1926

38. BARNES, A. R. Cerebral manifestations of paroxysmal tachycardia. *Am. J. M. Sc.* 171.489, 1926.

39 BARNES, A. R., and WILLIUS, F A. Cardiac pain in paroxysmal tachycardia *Am. Heart J.* 2:490, 1926.

40. BRAMS, W. H., and WOLF-BLITZSTEN, E. P. Paroxysmal tachycardia. *Med. Clinics North America* 9 1630, 1926.

41. CATTELL, McK. Observations on the action of digitalis on the frog heart and its modification by quinidine. *J. Pharmacol. & Exper. Therap.* 27.287, 1926.

42. CATTELL, McK., and CATTELL, H. A comparative study of the action of cinchona bark alkaloids on the isolated frog heart. *J. Pharmacol. & Exper. Therap.* 27:260, 1926.

43. OTTO, H. L., and GOLD, H Persistent premature contractions. *Arch. Int. Med.* 38.186, 1926.

44. WILSON, F. N., and WISHART, S. W. The effects produced by the intravenous injection of quinidine and other drugs upon the mechanism of the heart beat. *Tr. A. Am. Physicians* 41:55, 1926.

1927

45. LEVINE, S. A., and STEVENS, W. B. The therapeutic value of quinidine in coronary thrombosis complicated by ventricular tachycardia. *Am. Heart J.* 3 253, 1927.

46. WEISS, S., and HATCHER, R. A. III Studies on quinidin. *J. Pharmacol. & Exper. Therap.* 30.335, 1927.

1928

47. BRAM, I. Tolerance for quinine in exophthalmic goiter. *Arch. Int. Med* 42.53, 1928.

48. BRAMWELL, J. C., and ELLIS, R. The ultimate results of quinidine therapy in auricular fibrillation *Lancet* 2.960, 1928.

74. Gold, H., Otto, H. L., and Satchwell, H. The use of quinidine in ambulatory patients for the prevention of paroxysms of auricular flutter and fibrillation, with especial reference to dosage and the effects on intraventricular conduction. *Am. Heart J.* 9:219, 1933.

1934

75. Jezer, A., and Schwartz, S. P. Unusual manifestations following the use of quinidine sulphate in a patient with auricular flutter. *Am. Heart J.* 10:124, 1934.

76. Kwit, N. T., and Gold, H. Further experimental observations on the combined effects of digitalis and quinidine on the heart. *J. Pharmacol. & Exper. Therap.* 50 180, 1934.

77. Maher, C. C., Sullivan, C. P., and Scheribel, C. P. The effect of quinidin sulphate upon the electrocardiograms of patients with regular sinus mechanism. *Am. J. M. Sc.* 187:23, 1934.

78. Nathanson, M. H. Modification of vagus inhibition of the heart by quinidine. *Proc. Soc. Exper. Biol. & Med.* 31:1234, 1934.

79 Schwartz, S. P., and Jezer, A. The action of quinine and quinidine on patients with transient ventricular fibrillation. *Am. Heart J* 9:792, 1934.

1935

80. Carter, J B, and Traut, E. F. Quinidin and strychnin in the treatment of premature contractions. *Am J. M. Sc.* 189.206, 1935

81. Kohn, C M, and Levine, S. A. Evaluation of the use of quinidine sulfate in persistent auricular fibrillation. *Ann. Int Med.* 8 923, 1935.

82. Stroud, W. D, and Laplace, L B. The significance and treatment of auricular fibrillation. *Internat Clin.* 1:13, 1935.

1936

83. Borg, J. F. The use of quinidin in diagnosis and treatment of obscure cardiac arrhythmias. *Tr. Am. Therap. Soc.* 36 88, 1936.

84. Hall, D A-V nodal rhythm following administration of quinidine in auricular fibrillation. *Brit. M. J.* 2:589, 1936.

1932

61. Anderson, J. P. The incidence of auricular fibrillation and results of quinidine therapy. *Am. Heart J.* 8:128, 1932.
62. Barker, P. S, Bohning, A. L., and Wilson, F. N. Auricular fibrillation in Graves' disease. *Am. Heart J.* 8.121, 1932.
63. Barrier, C. W. Tachycardia. *Ann. Int. Med.* 5:829, 1932.
64. Campbell, M. Partial heart block due to quinidine. *Lancet* 2:1157, 1932.
65. Gold, H., and Modell, W. The action of quinidine on the heart in the normal unanesthetized dog. *J. Pharmacol & Exper. Therap.* 46:357, 1932.
66. Gold, H., Modell, W., and Price, L. Combined actions of quinidine and digitalis on the heart· an experimental study. *Arch Int. Med.* 50:766, 1932.
67. Levine, H D. The effect of quinidine sulphate in inhibiting ventricular fibrillation. *Arch. Int. Med.* 49:808, 1932.
68. McMillan, T. M., and Bellet, S. Auricular flutter: some of its clinical manifestations and its treatment. *Am. J. M. Sc.* 184 33, 1932.

1933

69. Bellet, S., Ravdin, I. S., McMillan, T. M., and Morrison, J. L. The rôle of the liver in the tolerance of the dog to quinidin. *Am. J. M. Sc.* 185.636, 1933.
70. Dawson, W. T., Sanders, J. P., and Tomlinson, L. M. Differentiation of optically isomeric and related cinchona alkaloids by quinine-sensitive subjects. *J. Immunology* 24 173, 1933.
71. Ernstene, A. C., and Lowis, S. The mechanism of vomiting induced by quinidine. I. Quinidine emesis in animals with denervated hearts. *J. Pharmacol. & Exper. Therap.* 48·305, 1933
72. Ernstene, A. C., and Lowis, S The mechanism of vomiting induced by quinidine. II. *J. Pharmacol. & Exper. Therap.* 48.359, 1933.
73. Escamilla, R. F. Report of a case of paroxysmal ventricular fibrillation in relation to quinidine therapy. *Am. Heart J.* 8.850, 1933.

1940

96. Breu, W., and Zollner, S. Chinidin als Antigen. *Wien. klin. Wchnschr.* 53 524, 1940.
97. Smith, F. H., McEachern, C. G., and Hall, G. E. The effect of the intravenous administration of quinidine sulfate on the development of ventricular fibrillation following sudden occlusion of the circumflex branch of the left coronary artery. *Am. Heart J.* 20 620, 1940.
98. Weisman, S. A. Studies on the time required for the elimination of quinidine from the heart and other organs. *Am. Heart J.* 20.21, 1940.
99. Wiggers, C. J. Physiologic basis for cardiac resuscitation from ventricular fibrillation: Method for serial defibrillation. *Am. Heart J.* 20.413, 1940

1941

100. Riseman, J. E. F., and Linenthal, H Paroxysmal ventricular tachycardia its favorable prognosis in the absence of acute cardiac damage, and its treatment with parenterally administered quinine dihydrochloride. *Am. Heart J.* 22:-219, 1941.

1942

101. Dubbs, A. W., and Parmet, D. H. Ventricular tachycardia stopped on the twenty-first day by giving quinidine sulfate intravenously *Am. Heart J* 24·272, 1942.
102. Goldschlag, F. A case of drug allergy of both types fixed and generalized eruption. *Med. J. Australia* 2.501, 1942
103. Rakov, H. L. Ventricular fibrillation in acute coronary artery thrombosis during intravenous administration of quinidine sulfate, report of a fatal case. *Ann Int. Med.* 16 571, 1942.
104. Wedd, A M, Blair, H. A., and Gosselin, R E. The action of quinidine on the cold blooded heart. *J. Pharmacol. & Exper. Therap* 75 251, 1942.
105. Wégria, R., and Nickerson, N. D. The effect of papaverine, epinephrine and quinidine on the fibrillation threshold of mammalian ventricles. *J. Pharmacol. & Exper. Therap.* 75·50, 1942.

85. Kurtz, C. M., Bennett, J. H., and Shapiro, H. H. Electrocardiographic studies during surgical anesthesia. *J.A.M.A.* 106:434, 1936.

86. Mautz, F. R. Reduction of cardiac irritability by the epicardial and systemic administration of drugs as a protection in cardiac surgery. *J. Thoracic Surg.* 5.612, 1936.

87. Starr, I., Jr. Antagonism between cardiac action of acetyl-β-methylcholine and acetylcholine, and that of quinidine. *J. Pharmacol. & Exper. Therap.* 56:77, 1936.

1937

88. Beck, C. S., and Mautz, F. R. The control of the heart beat by the surgeon with special reference to ventricular fibrillation occurring during operation. *Ann. Surg.* 106:525, 1937.

89. Hepburn, J., and Rykert, H. E. The use of quinidine sulfate intravenously in ventricular tachycardia. *Am. Heart J.* 14.620, 1937.

90. Jourdonais, L. F., and Mosenthal, H. O. Complete auriculoventricular block and auricular flutter with observations of the effect of quinidine sulfate. *Am. Heart J.* 14:735, 1937.

1938

91. Fahr, G. The treatment of cardiac irregularities. *J.A.M.A.* 111:2268, 1938.

92. Gouley, B. A., and Soloff, L. The use of quinidine in the treatment of arrhythmias and tachycardias caused by digitalis intoxication, with a note on the possibility of "spontaneous redigitalization" following rapid diuresis. *Am. Heart J.* 16:561, 1938.

1939

93. Messeloff, C. R. Observations on the use of quinidine sulfate in children *J. Lab. & Clin. Med.* 24:574, 1939.

94. Rosenbaum, F. F., and Levine, S. A. Auricular standstill: its occurrence and significance. *Am. J. Med. Sc.* 198:774, 1939.

95. Van Dongen, K. The action of (para)sympatol on fibrillation of the heart. *Arch. Int. Pharmacodyn* 62:261, 1939.

116. Thomas, W. O., and Harrison, T. R. The effect of quinidine on the mortality of rats with experimental myocardial injury. *Am. J. M. Sc.* 208·756, 1944.

1945

117. Carter, J. B. Uses and abuses of quinidine. *M. Clin. North America* 29 215, 1945.
118. Cornell Conferences on Therapy: Uses and abuses of quinidine. *New York State J. M.* 45:1, 1945.
119. Chapman, D. W. Observations on two patients with paroxysmal ventricular tachycardia treated by intravenous quinidine lactate. *Am. Heart J.* 30 276, 1945.
120. Hiatt, E., Brown, D., Quinn, G, and MacDuffie, K. The blocking action of the cinchona alkaloids and certain related compounds on the cardio-inhibitory vagus endings of the dog. *J. Pharmacol & Exper Therap* 85 55, 1945.
121. Kelsey, F. E, Oldham, F. K, and Geiling, E. M. K. Studies on antimalarial drugs, metabolism of quinine and quinidine in birds and mammals *J. Pharmacol. & Exper. Therap.* 85 170, 1945.
122. Scott, C. C., Anderson, R. C., and Chen, K. K. Comparison of the pharmacologic action of quinidine and dihydroquinidine. *J Pharmacol & Exper. Therap.* 84 184, 1945
123. Zimmerman, S L. Ventricular tachycardia a report of ten cases, eight of which were treated with quinidine with recovery in seven. *Ann. Int. Med.* 23 634, 1945.

1946

124. Askey, J. M. Quinidine in the treatment of auricular fibrillation in association with congestive failure *Ann. Int. Med.* 24·371, 1946.
125. Dawes, G S. Synthetic substitutes for quinidine. *Brit. J Pharmacol.* 1 90, 1946.
126. Delevett, A. F., and Poindexter, C. A. Plasma concentration of quinidine with particular reference to therapeutically effective levels in two cases of paroxysmal nodal tachycardia. *Am Heart J.* 32 697, 1946.
127. Gold, H, Modell, W., Otto, H. L, and Hanlon, L. W. Comparison of cinchona alkaloids on the circus rate of the

106. WEISMAN, S. A. A study of the analeptic value of certain drugs in the treatment of quinidine depression. *Am. Heart J.* 24.240, 1942.

107. WHITE, P. D., and BLUMGART, H. L. Cessation of repeated pulmonary infarction and of congestive failure after termination of auricular fibrillation by quinidine therapy. *J. Mt. Sinai Hosp.* 8:1095, 1942.

1943

108. ALSEVER, W. D. Treatment of paroxysmal auricular tachycardia in infancy and childhood. *J. Pediat.* 22:459, 1943.

109. BARKER, P. S., JOHNSTON, F. D, and WILSON, F. N. The effect of quinidine upon sinus tachycardia, including the production of transient bundle branch block. *Am. Heart J.* 25:760, 1943.

110. BRODIE, B. B., and UDENFRIEND, S. The estimation of quinine in human plasma with a note on the estimation of quinidine *J. Pharmacol. & Exper. Therap.* 78 154, 1943.

111. SAGALL, E. L., HORN, C. D., and RISEMAN, J. E. F. Studies on the action of quinidine in man; measurement of the speed and duration of effect following oral and intramuscular administration. *Arch. Int Med.* 71 460, 1943.

112. SCHIMERT, G., JR. Experimentelle Untersuchungen über die Wirkung des Chinidins auf die Coronardurchblutung des regelmässig und unregelmassig schlagenden Herzens. *Klin. Wchnschr.* 22:436, 1943.

113. STURNICK, M. I, RISEMAN, J. E F., and SAGALL, E. L. Studies on the action of quinidine in man. II Intramuscular administration of a soluble preparation of quinidine in the treatment of acute cardiac arrhythmias. *J.A.M.A.* 121:917, 1943.

1944

114. HIATT, E. P. Plasma concentrations following the oral administration of single doses of the principal alkaloids of cinchona bark. *J. Pharmacol. and Exper. Therap.* 81:160, 1944.

115. REICH, N. E. Successful use of massive dose of quinidine in a case of intractable ventricular tachycardia. *Am. Heart J.* 28:256, 1944.

Index

auricle in patients with auricular fibrillation. *Federation Proc.* 5:179, 1946.

128. Tandowsky, R. M., Oyster, J. M., and Silverglade, A. The combined use of lanatoside C and quinidine sulfate in the abolition of established auricular flutter. *Am. Heart J.* 32.617, 1946.

1947

129. Alexander, F., Gold, H., Katz, L. N., Levy, R. L., Scott, R., and White, P. D. The relative value of synthetic quinidine, dihydroquinidine, commercial quinidine, and quinine in the control of cardiac arrhythmias. *J. Pharmacol & Exper. Therap.* 90 191, 1947.

130. McMillan, R. L., and Welfare, C. R. Chronic auricular fibrillation: its treatment with quinidine sulfate. *J.A.M.A.* 135.1132, 1947.

1948

131. Cornell Conferences on Therapy: Management of disorders of cardiac rhythm. *Am. J. Med.* 5:110, 1948.

132. Glomset, D. J., and Birge, R. F. A morphologic study of the cardiac conduction system V. The pathogenesis of heart block and bundle branch block. *Arch. Path.* 45.135, 1948.

133. Herrmann, G. R., and Hejtmancik, M. R. A clinical and electrocardiographic study of paroxysmal ventricular tachycardia and its management. *Ann. Int. Med.* 28.989, 1948.

134. Nudelman, P. L., Leff, I. L., and Howe, C. D. Thrombopenic purpura following quinidine *J.A.M.A.* 137.1219, 1948.

135. Wégria, R Intensity and duration of action of quinidine sulfate in auricular fibrillation and flutter. *Am. Heart J.* 35 787, 1948

136. Wégria, R, and Boyle, M. N. Correlation between the effect of quinidine sulfate on the heart and its concentration in blood plasma. *Am. J. Med.* 4.373, 1948.

1949

137. Collins, V. J. Use of intravenous quinidine during clinical anesthesia for treatment of acute arrhythmias. *New York State J. Med.* 149:1554, 1949.